National Institute for Health and Care Excellence

Final

Type 1 diabetes in adults: diagnosis and management

[A] Evidence reviews for long-acting insulins in type 1 diabetes

NICE guideline NG17

Evidence reviews underpinning recommendations 1.7.3 to 1.7.9 in the NICE guideline

July 2021

Final

These evidence reviews were developed by Guideline Update Team

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-1389-3

Contents

.

1 Long-acting insulins for optimal diabetic control

1.1 Review question

In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus neutral protamine hagedorn (NPH)) and frequency of administration for optimal diabetic control?

1.1.1 Introduction

Basal insulin replacement needs to provide glucose control between meals and overnight, with minimal risk of hypoglycaemia. Long-acting insulins are basal insulins that mimic endogenous basal insulin secretion, but their duration of actions may last up to 36 hours.

The 2015 NICE guidance on type 1 diabetes in adults: diagnosis and management states that twice-daily insulin detemir should be offered as basal insulin therapy for adults with type 1 diabetes. However, an existing insulin regimen can be considered as an alternative basal insulin therapy if it is being used by the person and they are achieving their agreed targets. Additionally, once-daily insulin glargine or insulin detemir can be considered if twice daily basal insulin injections is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. Recommendations also state that other basal insulin regimens can be considered for adults with type 1 diabetes if other regimens recommended do not deliver agreed targets. Furthermore, when choosing an alternative insulin regimen, the person's preferences and acquisition cost should be taken into consideration.

The topic was reviewed by NICE'S surveillance team and new evidence was identified that supported the use of ultra-long-lasting degludec. This new evidence prompted a partial update of the guideline. The aim of this review is to determine the clinical and cost effectiveness of different long-acting insulin therapies and frequency of administration for diabetic control in adults with type 1 diabetes.

1.1.2 Table 1: Summary of the protocol

PICO Table	
Population	Adults (aged 18 years and older) with type 1 diabetes
Intervention	Long-acting insulins (once per day and twice per day regimens will be included): • Detemir (Levemir) • Degludec U100 (Tresiba) • Degludec U200 (Tresiba) • Glargine U100 (Lantus) • Glargine U300 (Toujeo) • NPH/ isophane/other intermediate (Humulin I, Insulatard, Insuman basal)) Biosimilar insulins, including but not limited to: • LY2963016 (Abasaglar) • MYL-1501D (Semglee)
Comparator	• Compared to each other • Same basal/long-acting insulin given either once/day or twice/day

PICO Table	

Outcomes	• HbA1c
	• Hypoglycaemia, including:
	  ○ Severe hypoglycaemia
	  ○ Nocturnal hypoglycaemia
	• Diabetic ketoacidosis
	• Time in target glucose range
	• Time spent in hypoglycaemic range
	• Quality of life, including patient satisfaction
	• Adverse events, including:
	  ○ Cancer (dichotomous)
	  ○ Injection site issues
	  ○ Weight gain/loss (continuous)
	• Hospital admissions including:
	  ○ Frequency of hospitalisations related to diabetes
	  ○ Ambulance call-outs
	• Mental health outcomes measured using validated questionnaires:
	  ○ Diabetes distress (including fear of hypoglycaemia, daily burden, treatment burden and diabetes burnout)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Insulin therapies of various strengths were included in this review:

- glargine U100
- glargine U300
- degludec U100
- degludec U200

Strength of the preparation can also be specified as units per millilitre (units/ml). For example, these insulins can also be written as glargine (100 units/ml), glargine (300 units/ml), degludec (100 units/ml) and degludec (200 units/ml). In this evidence review, units (U) has been used to highlight the strength of the preparation.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A total of 3,472 RCTs and systematic reviews were identified in the search. After removing duplicate references, 1,977 RCTs and systematic reviews were screened at title and abstract stage.

Following title and abstract screening, 211 studies were included for full text screening. These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). Overall, 51 studies were included.

The studies included examined the following interventions and frequencies of administration:

- Detemir vs NPH:
  - Detemir once daily vs NPH once daily
  - Detemir once/ twice daily vs NPH once/ twice daily
  - Detemir twice daily vs NPH twice daily
- Detemir vs Glargine U100:
  - Detemir twice daily vs glargine once daily
  - Detemir once/twice daily vs glargine once daily
- Degludec U100 vs Glargine U100:
  - Degludec U100 once daily vs glargine U100 once daily
- Degludec U200 vs Glargine U300:
  - Degludec U200 once daily vs glargine U300 once daily
- Degludec vs Glargine (concentration not defined)
  - Degludec once daily vs glargine twice daily
  - Degludec once daily vs glargine once daily
- Glargine U100 vs NPH:
  - Glargine U100 once daily vs NPH 4x daily
  - Glargine U100 once daily vs NPH once/ twice daily
  - Glargine U100 once daily vs NPH twice daily
  - Glargine U100 once daily NPH twice or more
- Degludec U100 vs Detemir:
  - Degludec U100 once daily vs detemir once daily
- Glargine U300 vs Glargine U100:
  - Glargine U300 once daily vs glargine U100 once daily

2 studies were also identified that compared frequency of administration. These studies examined the following frequencies:

- Glargine U100 once daily vs Glargine U100 twice daily
- Detemir once daily vs Detemir twice daily

Additionally, 5 studies were identified that compared the following glargine biosimilars to originator glargine:

- Glargine biosimilar (GP40061) vs glargine U100:
  - Biosim. once daily vs glargine U100 once daily
- Glargine biosimilar (MK-1293) vs glargine U100:
  - Biosim. once daily vs glargine U100 once daily
- Glargine biosimilar (MYL-1501D) vs glargine U100:
  - Biosim. once daily vs glargine U100 once daily
- Glargine biosimilar (LY2963016) vs glargine U100:
  - Biosim. once daily vs glargine U100 once daily

As these studies compared the effectiveness of glargine biosimilars to originator glargine, the committee were unable to form recommendations on the use of biosimilars.

See appendix E for evidence tables and the reference list in section 1.1.14.

1.1.4.2 Excluded studies

Overall, 160 studies were excluded. See appendix O for the list of excluded studies with reasons for their exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Detemir vs NPH

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Bartley 2008	RCT	• Aged 18 years and above
		• HbA1c ≤11.0%
		• BMI ≤35.0 kg/m²
		• History of Type 1 diabetes ≥1 year
		• Treated on a basal-bolus insulin regimen for ≥3 months
		• Able to self-measure plasma glucose
			Detemir
			Once or twice daily
			
			With insulin aspart
				NPH
				Once or twice daily
				
				With insulin aspart
					24 months	• HbA1c:
						  ○ HbA1c (%) at follow up
						  ○ Patients achieved HbA1c ≤7.0 %
						  ○ Patients achieved an HbA1c ≤7.0 % in the absence of confirmed hypoglycaemia.
						• Hypoglycaemia (all)
						  ○ Major hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious AE
						• Weight at follow up

De Leeuw 2005	RCT	• Aged 18 years and above • BMI 35 kg/m² • History of Type 1 diabetes -for 1 year • Treated on a basal-bolus insulin regimen for at least 2 months • Caucasian patients • HbA1c 12%	**Detemir** Twice daily With insulin aspart	**NPH** Twice daily With insulin aspart	12 months	• HbA1c: ○ Change in HbA1c (%) • Major hypoglycaemia • Nocturnal hypoglycaemia • Serious AEs • Injection site reactions • Change in body weight (kg)

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		• Total daily basal insulin requirement of 100 IU/day				
Hermanson 2001	Crossover RCT	• Aged 18 years and above • BMI <27.5 kg/m² • History of Type 1 diabetes -for over 2 years • Treated on a basal-bolus insulin regimen - NPH with human soluble insulin for at least 6 months • Caucasian patients • HbA1c ≤8.7% • Glucagon-stimulated C-peptide ≤0.1 nmol/l • NPH dose <40 IU/day	**Detemir** Once daily With human soluble insulin	**NPH** Once daily With human soluble insulin	6 weeks	• Hypoglycaemia (all) ○ Major hypoglycaemia

Home 2004	RCT	• Aged 18 years and above
		• BMI <35.5 kg/m²
		• History of Type 1 diabetes -for over 1 year
		• Treated on a basal-bolus insulin regimen- for over 2 months with basal insulin dose <100 units/day
		• HbA1c <12.0%
			Detemir
			Twice daily
			
			With insulin aspart
				NPH
				Twice daily
				
				With insulin aspart
					16 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						• Hypoglycaemia (all)
						  ○ Major hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Change in body weight (kg)

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
Kolendorf 2006	Crossover RCT	• Aged 18 years and above • BMI ≤35 kg/m² • History of Type 1 diabetes -for at least 1 year • Treated on a basal-bolus insulin regimen- for ≥4 months, with basal insulin (1, 2 or 3 times daily) in combination with mealtime aspart or lispro 3-4 times daily • HbA1c ≤9% • Total daily insulin dose ≤ 1.4 IU/kg per day and a basal insulin requirement ≥ 30% of the total daily insulin dose	**Detemir** Twice daily With insulin aspart	**NPH** Twice daily With insulin aspart	16 weeks	• HbA1c: ○ Change in HbA1c (%) • Hypoglycaemia (all) ○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia
Pieber 2005	RCT	• Aged 18 years and above • BMI -35 kg/m² • History of Type 1 diabetes ≥1 year • Treated on a basal-bolus insulin regimen for ≥ 2 months • Total daily basal insulin requirement of 100 IU/day • HbA1c -12%	**Detemir** Twice daily With insulin aspart	**NPH** Twice daily With insulin aspart	16 weeks	• HbA1c: ○ Change in HbA1c (%) • Hypoglycaemia (all) ○ Major hypoglycaemia ○ Nocturnal hypoglycaemia • Change in body weight (kg)

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Russell-Jones 2004	RCT	• Aged 18 years and above
		• History of Type 1 diabetes -For over 1 year
		• Treated on a basal-bolus insulin regimen
		• Already using basal or premixed insulin QD in the evening (between 5 PM and 11 PM) and human insulin before meals for over 2 months
			Detemir
			Once daily
			
			With human insulin
				NPH
				Once daily
				
				With human insulin
					6 months	• HbA1c:
						  ○ HbA1c (%) at follow up
						  ○ Change in HbA1c (%)
						• Hypoglycaemia (all)
						• Major hypoglycaemia
						• Nocturnal hypoglycaemia
						• Change in body weight (kg)

Standl 2004	RCT	• Aged 18 years and above
		• BMI ≤35.0 kg/m²
		• History of Type 1 diabetes - for over 12 months
		• Treated on a basal-bolus insulin regimen - for at least 2 months
		• Total daily basal insulin requirement of 100 IU/day
		• HbA1c ≤12%
			Detemir
			Twice daily
			
			With human insulin
				NPH
				Twice daily
				
				With human insulin
					12 months	• HbA1c:
						  ○ Change in HbA1c (%)
						• Hypoglycaemia (all)
						  ○ Major hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						• Injection site reaction

Vague 2003	RCT	• Patients with a history of type 1 diabetes for at least 1 year who had received basal (once or multiple daily) bolus insulin treatment for at least 2 months.	**Detemir**
			Twice daily
			
			With insulin aspart
				NPH
				Twice daily
				
				With insulin aspart
					6 months	• HbA1c:
						  ○ Change in HbA1c (%)
						• Hypoglycaemia (all)
						  ○ Major hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Injection site reaction

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		• Patients with HbA1c level less than or equal to 12%, a BMI less than or equal to 35kg/m2, and a total basal insulin dosage of less than or equal to 100 IU/day				• Change in body weight (kg)
Van Golen 2013	Crossover RCT	• Patients with type 1 diabetes, aged 18-60 years with a BMI of 18-35 kg/m^2	**Detemir** Twice daily With insulin aspart	**NPH** Twice daily With insulin aspart	12 weeks	• HbA1c: ○ Change in HbA1c (%) • Change in body weight (kg)

Zachariah 2011	Crossover RCT	• Patients with type 1 diabetes on a basal-bolus regimen
		• Type 1 diabetes duration > 12 months, on basal-bolus insulin regimen for > 3 months
		• age >18 years,
		• BMI <40 kg/m^2
		• HbA1c between 7.0 and 11.0%
			Detemir
			Once or twice daily
			
			With insulin aspart
				NPH
				Once or twice daily
				
				With insulin aspart
					16 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						• Hypoglycaemia (all)
						  ○ Major hypoglycaemia
						• Change in body weight (kg)

Table 3: Detemir vs Glargine U100

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Heller 2009	RCT	• Aged 18 years and above
		• HbA1c ≤11.0%
			Detemir
			Once or twice daily
				Glargine U100
				Once daily
					52 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						  ○ Patients achieved HbA1c ≤7.0 %

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

		• Treated on a basal-bolus insulin regimen- for at least 3 months	With insulin aspart	With insulin aspart		• Hypoglycaemia (all)
						  ○ Major hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious adverse events
						• Injection site reactions
						• Change in body weight (kg)

Pieber 2007	RCT	• Aged 18 years and above
		• BMI ≤35 kg/m²
		• History of Type 1 diabetes - For at least 1 year
		• HbA1c 7.5% - 12.0%
			Detemir
			Twice daily
			
			With insulin aspart
				Glargine U100
				Once daily
				
				With insulin aspart
					26 weeks	• HbA1c:
						  ○ HbA1c (%) at follow up
						• Hypoglycaemia (all)
						  ○ Severe hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Serious AEs
						• Change in weight (kg)

Renard 2011	Crossover RCT	• History of Type 1 diabetes - For more than 3 years, defined by a C-peptide concentration of < 0.1 nmol/L and a fasting blood glucose (FBG) ‡ 7 mmol/L. • Treated on a basal-bolus insulin regimen- For at least 6 months with glargine as basal insulin • HbA1c ≤8.5%	**Detemir** Once or twice daily With insulin glulisine	**Glargine U100** Once daily With insulin glulisine	16 weeks	• HbA1c: ○ Change in HbA1c (%) • Severe hypoglycaemia • Adverse events • Serious AEs

Table 4: Degludec U100 vs Glargine U100

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Birkeland 2011
 	
Home 2012
	RCT	• Patients aged 18-75 years of age diagnosed with type 1 diabetes ≥12 months before study
		• treated continually with insulin using any regimen
		• having an A1C of 7.0-11.0%.
			Degludec U100
			Once daily
			
			With insulin aspart
				Glargine U100
				Once daily
				
				With insulin aspart
					16 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						• Hypoglycaemia (all)
						  ○ Severe hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Serious adverse events
						• Change in weight (kg)
						• QoL - Measured using SF-36 version 2.

Heller 2012
 	
Bode 2013
	RCT	• Aged 18 years and above
		• BMI ≤35 kg/m²
		• History of Type 1 diabetes - For at least 1 year
		• Treated on a basal-bolus insulin regimen- For at least 1 year
		• HbA1c ≤10%
			Degludec U100
			Once daily
			
			With insulin aspart
				Glargine U100
				Once daily
				
				With insulin aspart
					52 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						  ○ Patients achieved HbA1c ≤7.0 %
						• Hypoglycaemia (all)
						  ○ Severe hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious AEs
						• Injection site reactions
						• Change in weight (kg)

Heise 2012	RCT	• Aged 18 years and above • BMI - 18.0-28.0 kg/m² • History of Type 1 diabetes -for a minimum of 12 months • Treated on a basal-bolus insulin regimen • treated with multiple daily insulin injections	**Degludec U100** Once daily With insulin aspart	**Glargine U100** Once daily With insulin aspart	12 days	• Serious hypoglycaemia • Nocturnal hypoglycaemia • Serious AEs • Injection site reaction

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		≥12 months (total daily insulin <1.2 U/kg/day and daily basal insulin ≥0.2 U/kg/day) • HbA1c ≤10.0%				

Lane 2017	Crossover RCT	• Aged 18 years and above
		• BMI ≤45 kg/m²
		• History of Type 1 diabetes - for a year or more
		• Treated on a basal-bolus insulin regimen
		• Treated with either a basal-bolus regimen or continuous subcutaneous insulin infusion for 26 weeks or more
		• HbA1c ≤10%
		• Fulfilled at least 1 of the pretrial risk criteria for developing hypoglycaemia: (1) experienced 1 or more severe hypoglycaemic episodes within the last year (based on ADA definition); (2) had moderate chronic renal failure (estimated glomerular filtration rate 30-59 mL/min/1.73 m2); (3) were unaware of
			Degludec U100
			Once daily
			
			With insulin aspart
				Glargine U100
				Once daily
				
				With insulin aspart
					32 weeks	• Hypoglycaemia (all)
						  ○ Severe hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious AEs
						• Change in weight (kg)

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		their hypoglycaemic symptoms; (4) had diabetes for more than 15 years; or (5) had an episode of hypoglycaemia (symptoms, blood glucose level of ≤70 mg/dL, or both) within the last 12 weeks				

Mathieu 2013	RCT	• Aged 18 years and above
		• BMI <35.0 kg/m²
		• Treated on a basal-bolus insulin regimen
		• HbA1c ≤10%
			Degludec U100
			Once daily
			
			With insulin aspart
				Glargine U100
				Once daily
				
				With insulin aspart
					26 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						• Hypoglycaemia (all)
						  ○ Severe hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious adverse events
						• Injection site reaction
						• Change in weight (kg)

Table 5: Degludec U200 vs Glargine U300

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Heise 2017	Crossover RCT	• Aged 18 years and above
		• BMI -18.5-29.0 kg.m²
		• HbA1c <9.0%
		• Multiple daily insulin injections or continuous s.c. insulin infusion for ≥12 months (total daily insulin <1.2 U/kg/d) and
			Degludec U200
			Once daily
			
			With insulin aspart
				Glargine U300
				Once daily
				
				With insulin aspart
					12 days	• Hypoglycaemia (all)
						  ○ Severe hypoglycaemia
						• Adverse events
						  ○ Serious AEs

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		a daily basal insulin requirement ≥0.2 U/kg/d				

Table 6: Degludec vs Glargine (concentration not defined)

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
Iga 2017	Crossover RCT	• History of Type 1 diabetes- for at least 1 year • Aged 20 years and older • Proliferative retinopathy or maculopathy • Pregnant or breast-feeding women • History or presence of cancer • History of cardiovascular disease or stroke, or blood pressure beyond the normal range • Active infectious diseases	**Degludec (concentration not defined)** Once daily With insulin aspart	**Glargine (concentration not defined)** Once daily With insulin aspart	12 weeks	• HbA1c: ○ HbA1c (%) at follow up • Time spent in target glucose range (%) • Time spent in hypoglycaemia (%) • Time spent in nocturnal hypoglycaemia(%)
Onda 2017	Crossover RCT	• Treated on a basal-bolus insulin regimen - received insulin therapy with frequent insulin injections for P12 weeks and were receiving insulin analogues as bolus insulin	**Degludec (concentration not defined)** Once daily With bolus insulin (not specified)	**Glargine (concentration not defined)** Twice daily With bolus insulin (not specified)	4 weeks	• Time in hypoglycaemia (< 70mg/dL) during 24 hours (mins)

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		• HbA1c >6.9% but <9% • Being treated with diet therapy • Age 20 - 80 years				

Table 7: Glargine U100 vs NPH

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Bolli 2009	RCT	• Aged 18-60 years
		• BMI 18-26 mg/kg²
		• History of Type 1 diabetes for more than 3 years
		• Treated on a basal-bolus insulin regimen
		• Intensive insulin therapy (NPH twice or more daily and lispro or regular human insulin at mealtimes)
		• HbA1c 7 - 9%
			Glargine U100
			Once daily
			
			With lispro
				NPH
				Twice daily (or more)
				
				With lispro
					30 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						• Change in hypoglycaemia
						• Change in serious hypoglycaemia
						• Change in severe nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious AEs
						• QoL

Chatterjee 2007	Crossover RCT	• Aged 18 years and above • Age 18-75 years • BMI <45 kg/m² • History of Type 1 diabetes • On insulin for at least 6 months • HbA1c 6-11%	**Glargine U100** Once-daily (period 1) followed by twice-daily NPH (period 2)	**NPH** Twice-daily (period 1) followed by once-daily glargine (period 2)	16 weeks	• HbA1c ○ Change in HbA1c (%) • Hypoglycaemia (all) – Change in hypoglycaemia • Severe hypoglycaemia – Change in serious hypoglycaemia • Nocturnal hypoglycaemia- Change in severe nocturnal hypoglycaemia • Adverse events • Serious adverse events

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
						• Change in body weight (kg) • QoL

Fulcher 2005	RCT	• Aged 18-80 years
		• History of Type 1 diabetes
		• Treated with insulin for at least 1 year
		• HbA1c ≥8%
			Glargine U100
			
			Once-daily
			
			With insulin lispro
				NPH
				
				Once-daily
				
				With insulin lispro
					30 weeks	• Hypoglycaemia (all)
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious AEs
						• Injection site reactions

Home 2005	RCT	• ≥18 years of age • Type 1 diabetes for >1 year • Use of any mealtime insulin analog for ≥3 months	**Glargine U100** Once daily with mealtime insulin	**NPH** Once daily with mealtime insulin	6 months	• HbA1c: ○ Change in HbA1c (%) • Hypoglycaemia (all) • Nocturnal hypoglycaemia • Adverse events • Serious AEs • Injection site reaction • Change in body weight

Pieber 2000	RCT	• History of Type 1 diabetes
		• Treated on a basal-bolus insulin regimen for at least 1 year
			Glargine U100
			Includes (30 µg/ml) once per day with mealtime regular human insulin
				NPH
				Includes (80 µg/ml) once per day with mealtime regular human insulin
					4 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						• Hypoglycaemia (all)
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						• Injection site reactions

Porcellati 2004	RCT	• History of Type 1 diabetes
		• Treated on a basal-bolus insulin regimen
		• Multiple daily combinations of lispro and NPH insulin at each meal, and NPH at
			Glargine U100
			
			Once daily Insulin glargine at dinnertime
			
			With mealtime lispro
				NPH
				
				4 X daily at mealtimes and bedtime
				
				With mealtime lispro
					52 weeks	• Hypoglycaemia:
						  ○ Frequency of hypoglycaemia (all)
						  ○ Severe hypoglycaemia - no. of patients
						• Nocturnal hypoglycaemia – frequency of nocturnal hypoglycaemia

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		bedtime, for at least 2 years • Free of any detectable microangiopathic complication • Negative at the screening for autonomic neuropathy				
Raskin 2000	RCT	• People with type 1 diabetes • Aged 18-80 years • Had been receiving treatment with NPH insulin with at least 1 year and insulin lispro for at least 3 months. • Patients had to have a serum C-peptide level ≤9mg/dl (0.5mmol/l) in the presence of a blood glucose level ≥99.0mg/dl (5.5mmol/l) and a Ghb value ≤12.0%.	**Glargine U100** Once-daily With mealtime insulin lispro	**NPH** Either once or twice per day With mealtime insulin lispro	12 weeks	• HbA1c: ○ Change in HbA1c (%) • Hypoglycaemia: ○ Hypoglycaemia ○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events • Injection site reactions
Ratner 2000	RCT	• Aged 18-80 years • With type 1 diabetes (post prandial C-peptide levels of ≤0.5nmol/l) for at least 1 year and GHb levels of ≤12.0%.	**Glargine U100** Once daily (at bedtime) Subjects used regular insulin ~30 mins before meals to meet	**NPH** Once daily (at bedtime) or twice daily (at bedtime and before breakfast) depending on their pretreatment insulin regimens.	28 weeks	• HbA1c: ○ Change in HbA1c (%) • Hypoglycaemia (all) ○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events ○ Serious AEs • Injection site reaction

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
			prandial insulin requirements	Subjects used regular insulin ~30 mins before meals to meet prandial insulin requirements.		
Rosenstock 2000	RCT	• People with type 1 diabetes • Aged 18 to 70 years • BMI of 18-28kg/m2 • HbA1c of <10% • Postprandial serum C-peptide of <0.2pmol/ml. • All study patients had been on a basal-bolus multiple daily insulin regimen for at least 2 months	**Glargine U100** Once daily at bedtime Injections of regular insulin were administered 30 mins before meals according to the patients' usual practice	**NPH** NPH insulin contained 100 U/ml. Given either once daily (at bedtime) or twice daily (before breakfast and at bedtime). Injections of regular insulin were administered 30 mins before meals according to the patients' usual practice.	4 weeks	• HbA1c: ○ Change in HbA1c (%) • Hypoglycaemic (all)

Rossetti 2003	RCT	• People with type 1 diabetes
		• Fasting plasma C-peptide ≤0.15 nmol/l on intensified treatment with multiple daily combinations of lispro and NPH insulin at each
			Glargine U100
			
			Once a day
			
			Mealtime lispro insulin was continued
				NPH
				
				Once a day
				
				Mealtime lispro insulin was continued
					3 months	• HbA1c:
						  ○ Change in HbA1c (%)
						• Hypoglycaemia
						  ○ Frequency of mild hypoglycaemia
						  ○ Severe hypoglycaemia

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		meal and NPH at bedtime.				
Witthaus 2001	RCT	• People with Type 1 diabetes • A minimum experience of one year of previous insulin use	**Glargine U100** Administered by subcutaneous injection once daily at bedtime In addition to glargine, regular insulin was administered before each meal	**NPH** Administered by subcutaneous injection either once or more than once, depending on the regimen followed prior to the study. In addition to NPH, regular insulin was administered	28 weeks	• QoL

Table 8: Glargine U300 vs Glargine U100

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
Bergenstal 2017	Crossover RCT	• Adult participants (≥18 and <70 years of age at screening) • Diagnosed with type 1 diabetes • Receiving any basal insulin regimen and mealtime insulin analog for at least 1 year	**Glargine U300** Once daily (period 1) followed by glargine U100 once daily (period 2)	**Glargine U100** Once daily (period 1) followed by glargine U300 once daily (period 2)	16 weeks (Two 8 week crossover periods)	• HbA1c: ○ Change in HbA1c (%) • Severe hypoglycaemia • Nocturnal hypoglycaemia • Adverse events • % time spent in target glucose range • CGM glucose range of 80–140 mg/dL (4.4–7.8 mmol/L)
Home 2015	RCT	• ≥18 years of age	**Glargine U300**	**Glargine U100**	6 months and 12 months	• HbA1c:

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
Home 2018		• Type 1 diabetes for >1 year • Use of any mealtime insulin analogue for ≥3 months.	Once daily With mealtime insulin	Once daily With mealtime insulin		○ Change in HbA1c (%) ○ % of participants achieving HbA1c <7.0% • Hypoglycaemia (all) ○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events ○ Serious AEs • Injection site reaction • Change in body weight • QoL
Jinnouchi 2015	RCT	• Japanese people of at least 20 years of age • With T1DM • Who were being treated with basal–bolus insulin • Glycated haemoglobin (HbA1c) within the range 6.5–10.0% • Median fasting self-monitored plasma glucose (SMPG) concentration of ≤13 mmol L-1 (240 mg dL-1) in the 3 days prior to randomisation	**Glargine U300** Once daily (period 1) Glargine U100 once daily (period 2) With mealtime insulin	**Glargine U100** Once daily (period 1) Glargine U300 once daily (period 2) With mealtime insulin	8.4 weeks	• Hypoglycaemia (all) ○ Nocturnal hypoglycaemia • Adverse events
Matsuhisa 2016 A	RCT	• Adults ≥18 years with type 1 diabetes • Receiving basal and mealtime insulin for ≥1 year	**Glargine U300** Once daily	**Glargine U100** Once daily	6 months	• HbA1c: ○ Change in HbA1c (%) ○ % of participants achieving HbA1c <7.0% • Hypoglycaemia (all)

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
		• HbA1c ≥7.0 and ≤10.0 % (≥53 and ≤86mmol/mol)	With mealtime insulin	With mealtime insulin		○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events ○ Serious adverse events • Injection site reactions • Change in body weight (kg)
Matsuhisa 2016 B	RCT	• Adults ≥18 years with type 1 diabetes • Receiving basal and mealtime insulin for ≥1 year • HbA1c ≥7.0 and ≤10.0 % (≥53 and ≤86mmol/mol)	**Glargine U300** Once daily With mealtime insulin	**Glargine U100** Once daily With mealtime insulin	12 months	• HbA1c: ○ Change in HbA1c (%) • Hypoglycaemia (all) ○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events • Injection site reactions • Change in body weight (kg)
Pettus 2019	RCT	• Aged ≥18 to ≤70 years at screening • Diagnosed with T1D ≥1 year prior to screening • On a stable dose of basal insulin analogue plus mealtime insulin for ≥1 year prior to screening • Had a daily basal insulin analogue dose of ≤80 units within 30 days of screening	**Glargine U300** Once daily With rapid mealtime insulin	**Glargine U100** Once daily With rapid mealtime insulin	16 weeks	• HbA1c: ○ Change in HbA1c (%) ○ % of participants achieving HbA1c >7% • Hypoglycaemia (all) ○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events ○ Serious AE • Injection site reactions • % time spent in target glucose range

Table 9: Degludec U100 vs Detemir

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
Davies 2014	RCT	• Aged 18 years and above (20 years and over for Japan) • BMI ≤35.0 kg/m² • History of Type 1 diabetes for at least 12 months • Treated on a basal-bolus insulin regimen for at least 12 months • HbA1c ≤10%	**Degludec U100** Once daily With mealtime insulin aspart	**Detemir** Once daily With mealtime insulin aspart	26 weeks	• HbA1c: ○ Change in HbA1c (%) ○ Proportion of participants with HbA1c <7.0% • Hypoglycaemia (all) ○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events ○ Serious adverse events • Injection site reactions • Change in body weight (kg)
Iwamoto 2013	RCT	• Aged 20 years and over • BMI <30.0 kg/m² • History of Type 1 diabetes for at least 12 months • Treated on a basal-bolus insulin regimen for at least 12 months • With either glargine or NPH as the basal insulin and aspart as the bolus component • HbA1c <10.4%	**Degludec U100** Once daily With mealtime insulin aspart	**Detemir** Once daily With mealtime insulin aspart	6 weeks	• Hypoglycaemia (all) ○ Serious hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events

Table 10: Glargine once daily vs glargine twice daily

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Ashwell 2006	Crossover RCT	• Aged 18 years and above (Aged 18-65 years)
		• History of Type 1 diabetes
		• Already taking insulin
		• Had been using a multiple insulin injection regimen for at least 1 year.
		• C-peptide concentration
		• Random concentration of ≤ 0.18 nmol/l
			Glargine U100
			Once daily
			
			With mealtime aspart
				Glargine U100
				Twice daily
				
				With mealtime aspart
					4 weeks	• Change in HbA1c (%)
						• Hypoglycaemia (all)
						  • Severe hypoglycaemia
						  • Nocturnal hypoglycaemia

Table 11: Detemir once daily vs Detemir twice daily

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Le Floch 2009	RCT	• History of Type 1 diabetes (For at least 1 year)
		• HbA1c 7.5-10%
			Detemir
			Once daily
			
			With mealtime aspart
				Detemir
				Twice daily
				
				With mealtime aspart
					4 months	• HbA1c:
						  ○ Change in HbA1c (%)
						  ○ Participants achieving HbA1c <7%
						• Frequency of hypoglycaemia (events per patient per 14 days)

See appendix E for full evidence tables.

Biosimilars

Table 12: LY IGlar vs Glargine U100

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
Blevins 2015	RCT	• T1DM duration of ≥ 1 year • Age ≥ 18 years • Receiving basal-bolus insulin therapy for ≥ 1 year before screening • HbA1c ≤11.0% • BMI ≤35kg/m2	**LY IGlar** Once daily Lispro used a mealtime insulin	**Glargine U100** Once daily Lispro used a mealtime insulin	Patients received treatment for 24 weeks. Patients continued to receive their assigned treatment for an extended period of 28 weeks (total duration of 52 weeks)	• HbA1c: ○ Change in HbA1c (%) (24 weeks and 52 weeks) ○ Participants achieving HbA1c < 7% • Hypoglycaemia (all) ○ Serious hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events ○ Serious AEs • Injection site reactions • Change in body weight (kg)
De Lozier 2018	RCT	• T1DM duration of ≥ 1 year • Age ≥ 18 years • Receiving basal-bolus insulin therapy for ≥ 1 year before screening • HbA1c ≤11.0% • BMI ≤35kg/m2	**LY IGlar** Once daily Lispro used a mealtime insulin	**Glargine U100** Once daily Lispro used a mealtime insulin	Patients received treatment for 24 weeks. Patients continued to receive their assigned treatment for an extended period of 28 weeks (total duration of 52 weeks)	• QoL

Table 13: MYLD-1501D vs Glargine U100

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes
Blevins 2018	RCT	• Established diagnosis of T1DM (according to American Diabetes Association 2014 criteria) • Treated with once-daily insulin glargine for ≥ 3months • Had an HbA1c ≤80 mmol/ mol (≤9.5%) at screening • Aged between 18 and 65 years • Had a fasting plasma C-peptide <0.3 nmol/L at screening • Had a stable weight for 3 months • BMI between 18.5 and 35.0 kg/m2 at screening	**MYLD-1501D** Once daily With mealtime insulin lispro 3 times a day	**Glargine U100** Once daily With mealtime insulin lispro 3 times a day	24 weeks and 52 weeks	• HbA1c: ○ Change in HbA1c (%) - week 24 and week 52 • Hypoglycaemia (all) ○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Adverse events • Change in body weight (kg)

Table 14: MK-1239 vs Glargine U100

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Home 2018	RCT	• ≥18 years of age
		• Type 1 diabetes for >1 year
		• Use of any mealtime insulin analogue for ≥3 months
			MK-1239
			
			Once daily
			
			With mealtime insulin
				Glargine U100
				
				Once daily
				
				With mealtime insulin
					1 year	• HbA1c:
						  ○ Change in HbA1c (%)
						  ○ Participants achieving HbA1c <7%%
						• Hypoglycaemia (all)
						  ○ Severe hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious AEs
						• Injection site reaction
						• Change in body weight

Table 15: GP40061 vs Glargine U100

Study	Study type	Population	Intervention	Comparator	Follow up	Outcomes

Karonova 2020	RCT	• Aged 18-65 years
		• BMI 18.5 - 30.0 kg/m²
		• History of Type 1 diabetes for at least 12 months
		• Treated on a basal-bolus insulin regimen for at least 30 days
		• HbA1c 6.5% - 12.0%
			GP40061 (GP-Gla (Glargine biosimilar))
			Once daily
			
			With bolus insulin (same bolus insulin as at baseline)
				Glargine U100 (Sa-Gla)
				Once daily
				
				With bolus insulin (same bolus insulin as at baseline)
					26 weeks	• HbA1c:
						  ○ Change in HbA1c (%)
						  ○ Participants achieving glycaemic goal
						• Hypoglycaemia
						  ○ Severe hypoglycaemia
						  ○ Nocturnal hypoglycaemia
						• Adverse events
						  ○ Serious AEs
						• Injection site reaction
						• Change in body weight (kg)
						• QoL

1.1.6 Summary of the effectiveness evidence

Table below summarises the results from the network meta-analysis (NMA). The columns list the insulin therapies, and the rows list the outcomes. Within each box, the insulin therapies listed represent results where there was a significant finding favouring that insulin. Boxes with dashes represent cases where the NMA could not differentiate between treatments. For further information see Appendix B. See appendix K for the full results of the NMA and appendix J for full GRADE tables.

Table 16: Summary of NMA results

Outcome	Treatments											Quality
	Detemir twice daily	NPH twice daily	Detemir once daily	NPH once daily	Detemir once/twice daily	NPH once/twice daily	Glargine U100 once daily	Degludec U100 once daily	NPH twice or more daily	Glargine U300 once daily	Glargine twice daily	
Change in HbA1c	-	-	-	-	-	-	-	-	-	-	-	Low
All hypoglycaemia	-	-	-	-	-	-	-	-	NA*	-	-	Very low
Severe/ major hypoglycaemia	-	-	-	-	-	• Detemir twice daily • Detemir once/twice daily	-	-	NA*	-	NA*	Very low
Nocturnal hypoglycaemia	-	• Detemir twice daily	• Degludec U100 once daily	• Degludec U100 once daily	-	-	• Degludec U100 once daily	-	NA*	-	-	Low

* *Outcome data unavailable.*

Tables below summarise the effect size and quality of evidence for outcomes not included in the NMA. Interpretation of effect is also summarised below and boxes that are shaded green highlight significant data. For further information see appendix B. See appendix I for full GRADE tables.

Detemir vs NPH

Table 17: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Hypoglycaemic episodes - Once/twice daily detemir vs Once/twice daily NPH *(MD less than 0 favours once/twice daily detemir)*					
1	RCT	44	MD: -0.30 (-4.61, 4.01)	Very low	Could not differentiate between long-acting insulins
Change in weight (kg) *(MD less than 0 favours detemir)*					
6	RCT	1799	MD: -0.86 (-1.29, -0.43)	Moderate	**Favours detemir**
Change in weight (kg) - Once daily detemir vs once daily NPH *(MD less than 0 favours once daily detemir)*					
2	RCT	803	MD: -0.79 (-1.49, -0.09)	Low	**Favours once daily detemir**
Change in weight (kg) – Once/twice daily detemir vs once/twice daily NPH *(MD less than 0 favours once/ twice daily detemir)*					
1	RCT	44	MD: -2.39 (-3.66, -1.12)	Low	**Favours once/twice daily detemir**
Change in weight (kg) – Twice daily detemir vs Twice daily NPH *(MD less than 0 favours twice daily detemir)*					
3	RCT	952	MD: -0.63 (-1.05, -0.21)	Moderate	**Favours twice daily detemir**
Injection site reactions – Twice daily detemir vs Twice daily NPH *(RR less than 1 favours twice daily detemir)*					
1	RCT	447	RR: 1.46 (0.15, 13.87)	Moderate	Could not differentiate between long-acting insulins

Table 18: Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) at follow up – Once/ twice daily detemir vs once/ twice daily NPH *(MD less than 0 favours once/twice daily detemir)*					
1	RCT	479	MD: -0.22 (-0.42, -0.02)	Moderate	**Favours once/twice daily detemir**
Patients achieving HbA1c ≤ 7% – Once/ twice daily detemir vs once/ twice daily NPH *(RR greater than 1 favours once/twice daily detemir)*					
1	RCT	479	RR: 1.32 (1.00, 1.74)	Moderate	**Favours once/twice daily detemir**
Patients achieving HbA1c ≤ 7% in the absence of confirmed hypoglycaemia- once/twice daily detemir vs once/twice daily NPH *(RR greater than 1 favours once/twice daily detemir)*					
1	RCT	479	RR: 1.66 (1.06, 2.60)	Moderate	**Favours once/twice daily detemir**
Change in weight (kg) *(MD less than 0 favours detemir)*					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
2	RCT	794	MD: -1.00 (-1.85, -0.15)	Moderate	**Favours detemir**
Change in weight (kg) – Once/twice daily detemir vs once/twice daily NPH *(MD less than 0 favours once/twice daily detemir)*					
1	RCT	479	MD: -0.99 (-1.88, -0.10)	Moderate	**Favours once/twice daily detemir**
Change in weight (kg) - Twice daily detemir vs twice daily NPH *(MD less than 0 favours twice daily detemir)*					
1	RCT	315	MD: -1.10 (-4.01, 1.81)	Low	Could not differentiate between long-acting insulins
Injection site reactions - Twice daily detemir vs twice daily NPH *(RR less than 1 favours twice daily detemir)*					
2	RCT	603	RR: 3.07 (0.86, 15.83)	Very low	Could not differentiate between long-acting insulins
Adverse events *(RR less than 1 favours detemir)*					
2	RCT	783	RR: 1.03 (0.36, 2.92)	Very low	Could not differentiate between long-acting insulins
Adverse events – Once/twice daily detemir vs once/twice daily NPH *(RR less than 1 favours once/twice daily detemir)*					
1	RCT	495	RR: 0.64 (0.40, 1.01)	Low	Could not differentiate between long-acting insulins
Adverse events – Twice daily detemir vs twice daily NPH *(RR less than 1 favours twice daily detemir)*					
1	RCT	288	RR: 1.85 (0.82, 4.15)	Very low	Could not differentiate between long-acting insulins
Serious AEs *(RR less than 1 favours detemir)*					
2	RCT	810	RR: 0.64 (0.32, 1.29)	Low	Could not differentiate between long-acting insulins
Serious AEs – Once/twice daily detemir vs once/twice daily NPH *(RR less than 1 favours once/twice daily detemir)*					
1	RCT	495	RR: 0.63 (0.29, 1.36)	Low	Could not differentiate between long-acting insulins
Serious AEs – Twice daily detemir vs twice daily NPH *(RR less than 1 favours twice daily detemir)*					
1	RCT	315	RR: 0.69 (0.12, 4.05)	Very low	Could not differentiate between long-acting insulins

Detemir vs Glargine U100

Table 19: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%)at follow up- Det: Twice daily vs IGlar: Once daily *(MD less than 0 favours twice daily detemir)*					
1	RCT	293	MD: -0.03 (-0.26, 0.20)	High	Could not differentiate between long-acting insulins
Change in weight (kg)- Det: Twice daily vs IGlar: Once daily *(MD less than 0 favours twice daily detemir)*					
1	RCT	293	MD: -0.44 (-1.15, 0.27)	High	Could not differentiate between long-acting insulins

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse events - Det: Once/twice daily vs IGlar: Once daily *(RR less than 1 favours once/twice daily detemir)*					
1	RCT	80	RR: 0.39 (0.04, 4.12)	Very low	Could not differentiate between long-acting insulins
Serious AEs *(RR less than 1 favours detemir)*					
2	RCT	373	RR: 0.53 (0.18, 1.58)	Very low	Could not differentiate between long-acting insulins
Serious AEs - Det: Twice daily vs IGlar: Once daily *(RR less than 1 favours twice daily detemir)*					
1	RCT	293	RR: 0.25 (0.03, 2.20)	Low	Could not differentiate between long-acting insulins
Serious AEs - Det: Once/twice daily vs IGlar: Once daily *(RR less than 1 favours once/twice daily detemir)*					
1	RCT	80	RR: 0.78 (0.21, 2.89)	Very low	Could not differentiate between long-acting insulins

Table 20: Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Patients achieving HbA1c ≤ 7% – Det: Once/twice daily vs IGlar: Once daily *(RR greater than 1 favour once/twice daily detemir)*					
1	RCT	443	RR: 1.08 (0.81, 1.45)	Low	Could not differentiate between long-acting insulins
Change in weight (kg) – Det: Once/twice daily vs IGlar: Once daily *(MD less than 0 favours once/twice detemir)*					
1	RCT	443	MD: -0.06 (-0.84, .72)	Moderate	Could not differentiate between long-acting insulins
Injection site reactions – Det: Once/twice daily vs IGlar: Once daily *(RR less than 1 favour once/twice daily detemir)*					
1	RCT	443	RR: 5.78 (1.38, 24.12)	Moderate	Could not differentiate between long-acting insulins
Adverse events – Det: Once/twice daily vs IGlar: Once daily *(RR less than 1 favour once/twice daily detemir)*					
1	RCT	443	RR: 1.03 (0.97, 1.10)	Low	Could not differentiate between long-acting insulins
Serious adverse events – Det: Once/twice daily vs IGlar: Once daily *(RR less than 1 favour once/twice daily detemir)*					
1	RCT	443	RR: 5.78 (0.76, 44.02)	Low	Could not differentiate between long-acting insulins

Degludec U100 vs Glargine U100

Table 21: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in weight (kg) - Once daily *(MD less than 0 favours once daily degludec U100)*					
3	RCT	948	MD: -0.40 (-0.88, 0.07)	Moderate	Could not differentiate between long-acting insulins
Injection site reactions – Once daily *(RR less than 1 favours once daily degludec U100)*					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
2	RCT	378	RR: 0.73 (0.17, 3.22)	Moderate	Could not differentiate between long-acting insulins
Adverse events - Once daily *(RR less than 1 favours once daily degludec U100)*					
1	RCT	326	RR: 1.25 (0.78, 2.01)	Moderate	Could not differentiate between long-acting insulins
Serious AEs - Once daily *(RR less than 1 favours once daily degludec U100)*					
3	RCT	496	RR: 0.82 (0.25, 2.64)	Moderate	Could not differentiate between long-acting insulins
QoL – Change in SF36 physical component scores – Once daily *(MD greater than 0 favours degludec U100)*					
1	RCT	118	MD: 0.67 (-2.31, 3.65)	Moderate	Could not differentiate between long-acting insulins
QoL – Change in SF36 mental component scores – Once daily *(MD greater than 0 favours degludec U100)*					
1	RCT	118	MD: 3.01 (0.31, 5.71)	Low	**Favours once daily degludec U100**

Table 22: Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Patients achieving HbA1c target (<7%, <53mmol/mol) – once daily *(RR greater than 1 favours once daily degludec U100)*					
1	RCT	629	RR: 0.93 (0.75, 1.15)	Moderate	Could not differentiate between long-acting insulins
Change in weight (kg) - Once daily *(MD less than 0 favours once daily degludec U100)*					
1	RCT	629	MD: 0.20 (-0.51, 0.91)	High	Could not differentiate between long-acting insulins
Injection site reaction– Once daily *(RR less than 1 favours once daily degludec U100)*					
2	RCT	629	RR: 0.51 (0.22, 1.15)	Low	Could not differentiate between long-acting insulins
Adverse events - Once daily *(RR less than 1 favours once daily degludec U100)*					
2	RCT	1230	RR: 0.94 (0.64, 1.40)	Low	Could not differentiate between long-acting insulins
Serious AEs – Once daily *(RR less than 1 favours once daily degludec U100)*					
2	RCT	1230	RR: 0.83 (0.59, 1.17)	Low	Could not differentiate between long-acting insulins

Degludec U200 vs Glargine U300

Table 23: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse events – Once daily *(RR less than 1 favours once daily degludec U200)*					
1	RCT	60	RR: 1.00 (0.51, 1.97)	Low	Could not differentiate between long-acting insulins

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Serious AEs - Once daily *(RR less than 1 favours once daily degludec U200)*					
1	RCT	60	Not estimable	Very low	Could not be estimated

Degludec vs Glargine (concentration not defined)

Table 24: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) at follow up – once daily *(MD less than 0 favours once daily degludec)*					
1	RCT	40	MD: -0.10 (-0.63, 0.43)	Very low	Could not differentiate between long-acting insulins
Percentage of time in target glucose range (70 and 140 mg/dL (3.9–7.8 mmol/L)) – once daily *(MD greater than 0 favours once daily degludec)*					
1	RCT	40	MD: 1.20 (-11.22, 13.62)	Very low	Could not differentiate between long-acting insulins
Time in hypoglycaemia (<70 mg/dL) during 24 hours (minutes) – IDeg: once daily vs IGlar: twice daily *(MD less than 0 favours once daily degludec)*					
1	RCT	26	MD: 47.70 (-118.12, 213.52)	Very low	Could not differentiate between long-acting insulins
Percentage of time spent in hypoglycaemia – once daily *(MD greater than 0 favours once daily degludec)*					
1	RCT	40	MD: 1.20 (-3.74, 6.14)	Very low	Could not differentiate between long-acting insulins
Percentage of time spent in nocturnal hypoglycaemia – once daily *(MD less than 0 favours once daily degludec)*					
1	RCT	40	MD: 4.50 (-12.90, 21.90)	Very low	Could not differentiate between long-acting insulins

Degludec U100 vs Detemir

Table 25: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Participants achieving HbA1c <7% - once daily *(RR greater than 1 favours once daily degludec U100)*					
1	RCT	453	RR: 1.10 (0.86, 1.41)	Moderate	Could not differentiate between long-acting insulins
Change in weight (kg) – once daily *(MD less than 0 favours once daily degludec U100)*					
1	RCT	453	MD: 1.10 (0.55, 1.65)	Moderate	**Favours detemir once daily**
Injection site reactions- once daily *(RR less than 1 favours once daily degludec U100)*					
1	RCT	453	RR: 2.02 (0.58, 7.05)	Low	Could not differentiate between long-acting insulins

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse events– once daily *(RR less than 1 favours once daily degludec U100)*					
2	RCT	518	RR: 1.15 (0.78, 1.70)	Low	Could not differentiate between long-acting insulins
Serious AEs- once daily *(RR less than 1 favours once daily degludec U100)*					
1	RCT	453	RR: 1.45 (0.67, 3.17)	Low	Could not differentiate between long-acting insulins

Glargine U100 vs NPH

Table 26: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in HbA1c (%)- Glargine: once daily vs NPH: 4 x daily- bedtime *(MD less than 0 favours once daily glargine U100)*					
1	RCT	34	MD: -0.50 (-0.89, -0.11)	Very low	**Favours glargine U100**
Change in HbA1c (%)- Glargine: once daily vs NPH: 4 x daily- dinnertime *(MD less than 0 favours once daily glargine U100)*					
1	RCT	34	MD: -0.51 (-0.90, -0.12)	Very low	**Favours glargine U100**
Frequency of mild hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily- bedtime *(MD less than 0 favours once daily glargine U100)*					
1	RCT	34	MD: -4.50 (-7.60, -1.40)	Very low	**Favours glargine U100**
Frequency of mild hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily- dinnertime *(MD less than 0 favours once daily glargine U100)*					
1	RCT	34	MD: -4.10 (-7.09, -1.11)	Very low	**Favours glargine U100**
Frequency of nocturnal hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily- bedtime *(MD less than 0 favours once daily glargine U100)*					
1	RCT	34	MD: -1.60 (-2.47, -0.73)	Very low	**Favours glargine U100**
Frequency of nocturnal hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily- dinnertime *(MD less than 0 favours once daily glargine U100)*					
1	RCT	34	MD: -1.90 (-2.78, -1.02)	Very low	**Favours glargine U100**
Change in weight (kg) - Glargine: once daily vs NPH: twice daily *(MD less than 0 favours once daily glargine U100)*					
1	RCT	120	MD: -0.24 (-4.97, 4.49)	Moderate	Could not differentiate between long-acting insulins
Injection site reactions - Glargine: once daily vs NPH: once or twice daily *(RR less than 1 favours once daily glargine U100)*					
2	RCT	739	RR: 1.14 (0.70, 1.85)	Low	Could not differentiate between long-acting insulins

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse events- Glargine: once daily, NPH: once or twice daily *(RR less than 1 favours once daily glargine U100)*					
1	RCT	103	RR: 1.31 (0.91, 1.89)	Low	Could not differentiate between long-acting insulins

Table 27: Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in hypoglycaemia (episodes/ patient/ month) – Glargine: once daily vs NPH: twice (or more) *(MD less than 0 favours once daily glargine U100)*					
1	RCT	175	MD: 0.05 (-1.47, 1.57)	Low	Could not differentiate between long-acting insulins
Change in severe hypoglycaemia (episodes/ patient/ month) – Glargine: once daily vs NPH: twice (or more) *(MD less than 0 favours once daily glargine U100)*					
1	RCT	175	MD: 0.00 (-0.60, 0.60)	Low	Could not differentiate between long-acting insulins
Change in severe nocturnal hypoglycaemia (episodes/ patient/ month) – Glargine: once daily vs NPH: twice (or more) *(MD less than 0 favours once daily glargine U100)*					
1	RCT	175	MD: -0.09 (-0.28, 0.10)	Low	Could not differentiate between long-acting insulins
Frequency of hypoglycaemia (episodes/ patient/ month) - Glargine: once daily vs NPH: 4 x daily *(MD less than 0 favours once daily glargine U100)*					
1	RCT	121	MD: -4.00 (-5.98, -2.04)	Low	**Favours glargine U100 once daily**
Frequency of nocturnal hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily *(MD less than 0 favours once daily glargine U100)*					
1	RCT	121	MD: -2.00 (-2.71, -1.29)	Moderate	**Favours glargine U100 once daily**
Injection site reactions *(RR less than 1 favours glargine U100)*					
3	RCT	1244	RR: 1.19 (0.81, 1.77)	Very low	Could not differentiate between long-acting insulins
Injection site reactions – once daily *(RR less than 1 favours once daily glargine U100)*					
1	RCT	125	RR: 0.73 (0.24, 2.16)	Very low	Could not differentiate between long-acting insulins
Injection site reactions - Glargine: once daily vs NPH: once or twice daily *(RR less than 1 favours once daily glargine U100)*					
2	RCT	1119	RR: 1.29 (0.84, 1.97)	Very low	Could not differentiate between long-acting insulins
Adverse events *(RR less than 1 favours glargine U100)*					
3	RCT	885	RR: 1.00 (0.83, 1.20)	Low	Could not differentiate between long-acting insulins
Adverse events - once daily *(RR less than 1 favours once daily glargine U100)*					
1	RCT	125	RR: 1.03 (0.92, 1.16)	Very low	Could not differentiate between long-acting insulins

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse events – Glargine: once daily vs NPH: once or twice daily *(RR less than 1 favours once daily glargine U100)*					
1	RCT	585	RR: 0.95 (0.63, 1.45)	Moderate	Could not differentiate between long-acting insulins
Adverse events- Glargine: once daily vs NPH: twice (or more) *(RR less than 1 favours once daily glargine U100)*					
1	RCT	175	RR: 1.06 (0.07, 16.66)	Very low	Could not differentiate between long-acting insulins
Serious AES *(RR less than 1 favours glargine U100)*					
3	RCT	834	RR: 1.43 (0.47, 4.41)	Low	Could not differentiate between long-acting insulins
Serious AES – Once daily *(RR less than 1 favours once daily glargine U100)*					
1	RCT	125	RR: 1.69 (0.42, 6.78)	Very low	Could not differentiate between long-acting insulins
Serious AEs- Glargine: once daily, NPH: twice (or more) *(RR less than 1 favours once daily glargine U100)*					
1	RCT	175	RR: 1.06 (0.07, 16.66)	Very low	Could not differentiate between long-acting insulins
Serious AEs- Glargine: once daily vs NPH: once or twice *(RR less than 1 favours glargine U100)*					
1	RCT	534	RR: 1.02 (0.06, 16.27)	Low	Could not differentiate between long-acting insulins
QoL – DTSQ- change in treatment satisfaction from baseline – Glargine: once daily vs NPH: once or more than once *(higher score indicating greater satisfaction)*					
1	RCT	517	MD: 1.83 (0.82, 2.84)	Moderate	Could not differentiate between long-acting insulins
QoL – DTSQ- change in perceived frequency of hyperglycaemia from baseline – Glargine: once daily vs NPH: once or more than once *(Lower score indicates greater satisfaction)*					
1	RCT	517	MD: -0.25 (-0.49, -0.01)	Moderate	**Favours glargine U100 once daily**
QoL – DTSQ- change in perceived frequency of hypoglycaemia from baseline – Glargine: once daily vs NPH: once or more than once *(Lower score indicates greater satisfaction)*					
1	RCT	517	MD: -0.05 (-0.27, 0.17)	Moderate	**Favours glargine U100 once daily**
QoL – W-BQ22- change in general wellbeing from baseline – Glargine: once daily vs NPH: once or more than once *(Higher score indicates greater wellbeing)*					
1	RCT	517	MD: -0.35 (-1.50, 0.80)	Moderate	Could not differentiate between long-acting insulins
QoL – W-BQ22- change in depression from baseline – Glargine: once daily vs NPH: once or more than once *(Lower score indicates greater wellbeing)*					
1	RCT	517	MD: 0.05 (-0.31, 0.41)	Moderate	Could not differentiate between long-acting insulins
QoL – W-BQ22- change in anxiety from baseline – Glargine: once daily vs NPH: once or more than once *(Lower score indicates greater wellbeing)*					
1	RCT	517	MD: 0.22 (-0.17, 0.61)	Moderate	Could not differentiate between long-acting insulins

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
QoL – W-BQ22- change in energy from baseline – Glargine: once daily vs NPH: once or more than once *(Higher score indicates greater wellbeing)*					
1	RCT	517	MD: -0.07 (-0.40, 0.26)	Moderate	Could not differentiate between long-acting insulins
QoL – W-BQ22- change in positive wellbeing from baseline – Glargine: once daily vs NPH: once or more than once *(Higher score indicates greater wellbeing)*					
1	RCT	517	MD: 0.04 (-0.39, 0.47)	Moderate	Could not differentiate between long-acting insulins

Glargine U300 vs Glargine U100

Table 28: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Patients achieving HbA1c <7% - once daily *(RR greater than 1 favour once daily glargine U300)*					
3	RCT	1336	RR:0.92 (0.76, 1.12)	Low	Could not differentiate between long-acting insulins
Percentage of time spent in target glucose range – once daily *(MD greater than 0 favours once daily glargine U300)*					
1	RCT	663	MD: 0.35 (-1.65, 2.35)	Moderate	Could not differentiate between long-acting insulins
Change in weight – once daily *(MD less than 0 favours once daily glargine U300)*					
2	RCT	792	MD: -0.50 (-0.89, -0.11)	Moderate	**Favours glargine U300 once daily**
Adverse events- once daily *(RR greater than 1 favour once daily glargine U300)*					
5	RCT	1588	RR: 1.08 (0.98, 1.19)	Low	Could not differentiate between long-acting insulins
Serious AEs - once daily *(RR greater than 1 favour once daily glargine U300)*					
3	RCT	1430	RR: 0.95 (0.61, 1.47)	Low	Could not differentiate between long-acting insulins
Injection site reactions – Once daily *(RR greater than 1 favour once daily glargine U300)*					
3	RCT	1430	RR: 1.67 (0.52, 5.33)	Low	Could not differentiate between long-acting insulins
QoL- Change in EQ-5D utility index– once daily *(Higher score indicates better QoL)*					
1	RCT	546	MD: 0.03 (0.00, 0.06)	Moderate	**Favours glargine U300 once daily**
QoL- Change in DTSQ – once daily *(Higher score indicates better satisfaction)*					
1	RCT	546	MD: -0.40 (-1.23, 0.43)	Moderate	Could not differentiate between long-acting insulins

Table 29: Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in weight (kg)- once daily *(MD less than 0 favours once daily glargine U300)*					
1	RCT	243	MD: -0.35 (-0.91, 0.21)	Moderate	Could not differentiate between long-acting insulins
Adverse events – once daily *(RR greater than 1 favour once daily glargine U300)*					
1	RCT	549	RR: 1.23 (0.85, 1.77)	Low	Could not differentiate between long-acting insulins
Serious AEs– once daily *(RR greater than 1 favour once daily glargine U300)*					
1	RCT	549	RR: 1.04 (0.62, 1.74)	Low	Could not differentiate between long-acting insulins
Injection site reaction- once daily *(RR greater than 1 favour once daily glargine U300)*					
2	RCT	792	RR: 2.01 (0.61, 6.59)	Low	Could not differentiate between long-acting insulins
QoL- Change in EQ-5D utility index- once daily *(Higher score indicates better QoL)*					
1	RCT	546	MD: 0.00 (-0.03, 0.03)	Moderate	Could not differentiate between long-acting insulins
QoL- Change in DTSQ– Once daily *(Higher score indicates better satisfaction)*					
1	RCT	546	MD: -0.30 (-1.16, 0.58)	Moderate	Could not differentiate between long-acting insulins
QoL- Change in HFSII score – Once daily *(lower score indicating less fear of hypoglycaemia)*					
1	RCT	549	MD: 0.00 (-0.07, 0.07)	Moderate	Could not differentiate between long-acting insulins

Detemir once daily vs Detemir twice daily

Table 30: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Participants achieving HbA1c <7% *(RR greater than 1 favours detemir twice daily)*					
1	RCT	512	RR: 0.92 (0.61, 1.39)	Moderate	Could not differentiate between long-acting insulins
Frequency of hypoglycaemia (events/ patient/ 14 days) *(MD less than 0 favours once daily detemir)*					
1	RCT	512	MD: -3.00 (-6.52, 0.52)	High	Could not differentiate between long-acting insulins

Biosimilars

Tables below summarise the effectiveness of biosimilars compared to glargine U100. These studies compared the effectiveness of glargine biosimilars to originator glargine and due to the NICE position statement on biosimilars, the committee were unable to form specific recommendations. .

LY IGlar vs Glargine U100

Table 31: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in HbA1c (%) – once daily *(MD less than 0 favours once daily LY IGlar)*					
1	RCT	535	MD: 0.11 (-0.03, 0.25)	Moderate	Could not differentiate between long-acting insulins
Participants achieving HbA1c <7% - once daily *(RR greater than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 1.07 (0.95, 1.03)	Low	Could not differentiate between long-acting insulins
Hypoglycaemia (all)– once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 0.99 (0.95, 1.03)	Low	Could not differentiate between long-acting insulins
Major/ severe hypoglycaemia – once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 0.62 (0.21, 1.88)	Low	Could not differentiate between long-acting insulins
Nocturnal hypoglycaemia – once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 1.02 (0.94, 1.11)	Low	Could not differentiate between long-acting insulins
Change in weight (kg) – once daily *(MD less than 0 favours once daily LY IGlar)*					
1	RCT	535	MD: 0.00 (-2.75, 2.75)	Moderate	Could not differentiate between long-acting insulins

Table 32: Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in HbA1c (%) – once daily *(MD less than 0 favours once daily LY IGlar)*					
1	RCT	535	MD: 0.02 (-0.15, 0.19)	Moderate	Could not differentiate between long-acting insulins
Participants achieving HbA1c <7% - once daily *(RR greater than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 1.20 (0.91, 1.59)	Low	Could not differentiate between long-acting insulins
Hypoglycaemia (all)– once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 0.99 (0.96, 1.02)	Low	Could not differentiate between long-acting insulins

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Major/ severe hypoglycaemia – once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 1.00 (0.44, 2.26)	Low	Could not differentiate between long-acting insulins
Nocturnal hypoglycaemia – once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 0.98 (0.91, 1.04)	Low	Could not differentiate between long-acting insulins
Change in weight (kg) – once daily *(MD less than 0 favours once daily LY IGlar)*					
1	RCT	535	MD: 0.00 (-2.74, 2.75)	Moderate	Could not differentiate between long-acting insulins
Adverse events– once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 1.21 (0.61, 2.40)	Low	Could not differentiate between long-acting insulins
Serious AEs- once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 0.83 (0.47, 1.47)	Low	Could not differentiate between long-acting insulins
Injection site reactions- once daily *(RR less than 1 favours once daily LY IGlar)*					
1	RCT	535	RR: 2.32 (0.61, 8.89)	Low	Could not differentiate between long-acting insulins
QoL – Change in ITSQ total score – once daily *(greater score indicates greater improvement)*					
1	RCT	535	MD: -0.16 (-2.89, 2.57)	Moderate	Could not differentiate between long-acting insulins
QoL – Change in ALBSS total score - once daily *(lower score indicates greater improvement)*					
1	RCT	535	MD: -0.69 (-3.98, 2.60)	Moderate	Could not differentiate between long-acting insulins

MYLD-1501D vs Glargine U100

Table 33: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
HbA1c (%) at follow up- once daily *(MD less than 0 favours once daily MYLD-1501D)*					
1	RCT	558	MD: 0.03 (-0.12, 0.18)	Moderate	Could not differentiate between long-acting insulins

Table 34: Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in HbA1c (%) – Once daily *(MD less than 0 favours once daily MYLD-1501D)*					
1	RCT	558	MD: -0.04 (-0.19, 0.11)	Moderate	Could not differentiate between long-acting insulins
Change in weight (kg) – once daily *(MD less than 0 favours once daily MYLD-1501D)*					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1	RCT	558	MD: 0.16 (-0.41, 0.73)	Moderate	Could not differentiate between long-acting insulins
Hypoglycaemia (all)– once daily *(RR less than 1 favours once daily MYLD-1501D)*					
1	RCT	558	RR: 0.90 (0.78, 1.04)	Low	Could not differentiate between long-acting insulins
Major/ severe hypoglycaemia – once daily *(RR less than 1 favours once daily MYLD-1501D)*					
1	RCT	558	RR: 0.84 (0.38, 1.84)	Low	Could not differentiate between long-acting insulins
Nocturnal hypoglycaemia – once daily *(RR less than 1 favours once daily MYLD-1501D)*					
1	RCT	558	RR: 1.13 (0.42, 3.09)	Low	Could not differentiate between long-acting insulins
Adverse events– once daily *(RR less than 1 favours once daily MYLD-1501D)*					
1	RCT	558	RR: 0.93 (0.87, 1.01)	Very low	Could not differentiate between long-acting insulins

MK-1239 vs Glargine U100

Table 35: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in HbA1c (%) – once daily *(MD less than 0 favours once daily MK-1239)*					
1	RCT	499	MD: 0.04 (-0.19, 0.27)	Low	Could not differentiate between long-acting insulins
Participants achieving HbA1c <7% - once daily *(RR greater than 1 favours once daily MK-1239)*					
1	RCT	499	RR:0.97 (0.76, 1.24)	Very low	Could not differentiate between long-acting insulins
Hypoglycaemia (all)– once daily *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 0.99 (0.98, 1.01)	Very low	Could not differentiate between long-acting insulins
Major/ severe hypoglycaemia – once daily *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 1.41 (0.89, 2.24)	Very low	Could not differentiate between long-acting insulins
Nocturnal hypoglycaemia – once daily *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 0.97 (0.93, 1.01)	Low	Could not differentiate between long-acting insulins
Change in weight (kg) – once daily *(MD less than 0 favours once daily MK-1239)*					
1	RCT	499	MD: 0.00 (-0.60, 0.60)	Low	Could not differentiate between long-acting insulins

Table 36: Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in HbA1c (%) – once daily *(MD less than 0 favours once daily MK-1239)*					
1	RCT	499	MD: -0.02 (-0.27, 0.23)	Low	Could not differentiate between long-acting insulins
Participants achieving HbA1c <7% - once daily *(RR greater than 1 favours once daily MK-1239)*					
1	RCT	499	RR:0.96 (0.71, 1.29)	Very low	Could not differentiate between long-acting insulins
Hypoglycaemia (all)– once daily *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 0.99 (0.98, 1.01)	Very low	Could not differentiate between long-acting insulins
Major/ severe hypoglycaemia – once daily *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 0.95 (0.65, 1.40)	Very low	Could not differentiate between long-acting insulins
Nocturnal hypoglycaemia – once daily *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 0.98 (0.95, 1.02)	Very low	Could not differentiate between long-acting insulins
Change in weight (kg) – once daily *(MD less than 0 favours once daily MK-1239)*					
1	RCT	499	MD: -0.30 (-1.02, 0.42)	Low	Could not differentiate between long-acting insulins
Adverse events – once daily *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 0.91(0.76, 1.08)	Very low	Could not differentiate between long-acting insulins
Serious AEs – once daily *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 0.82 (0.49, 1.37)	Very low	Could not differentiate between long-acting insulins
Injection site reactions *(RR less than 1 favours once daily MK-1239)*					
1	RCT	499	RR: 2.14 (0.20, 23.46)	Very low	Could not differentiate between long-acting insulins

GP40061 vs Glargine U100

Table 37: Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in HbA1c (%)– Once daily *(MD less than 0 favours once daily GP40061)*					
1	RCT	180	MD: 0.11 (-0.19, 0.41)	Moderate	Could not differentiate between long-acting insulins
Participants achieving glycaemic control– once daily *(RR greater than 1 favours once daily GP40061)*					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1	RCT	180	RR: 0.79 (0.43, 1.45)	Low	Could not differentiate between long-acting insulins
Change in weight (kg)- once daily *(MD less than 0 favours once daily GP40061)*					
1	RCT	180	MD: -0.20 (-0.80, 0.40)	Low	Could not differentiate between long-acting insulins
Major/ severe hypoglycaemia – once daily *(RR less than 1 favours once daily GP40061)*					
1	RCT	180	RR: 0.44 (0.14, 1.39)	Very low	Could not differentiate between long-acting insulins
Nocturnal hypoglycaemia – once daily *(RR less than 1 favours once daily GP40061)*					
1	RCT	180	RR: 0.82 (0.56, 1.19)	Very low	Could not differentiate between long-acting insulins
Adverse events – once daily *(RR less than 1 favours once daily GP40061)*					
1	RCT	180	RR: 1.50 (0.56, 4.04)	Very low	Could not differentiate between long-acting insulins
Serious AEs– once daily *(RR less than 1 favours once daily GP40061)*					
1	RCT	180	RR: 1.00 (0.14, 6.95)	Very low	Could not differentiate between long-acting insulins
Injection site reactions *(RR less than 1 favours once daily GP40061)*					
1	RCT	180	RR: 3.00 (0.32, 28.30)	Very low	Could not differentiate between long-acting insulins
QoL – Change in DTSQ total score – once daily *(higher score indicating greater satisfaction)*					
1	RCT	180	MD: 0.29 (-1.79, 2.37)	Very low	Could not differentiate between long-acting insulins

1.1.7 Economic evidence

1.1.7.1 Included studies

A systematic search was performed to identify economic evidence for the review question, with 1,000 papers identified. Following an initial review of titles and abstracts, 46 papers were selected for screening on full text. Following the full text review, 27 papers were identified as applicable cost-utility analyses for the review question and are summarised in section 1.1.8. The study selection is shown in more detail in appendix I, while full economic evidence tables along with the checklists for study applicability and study limitations are shown in appendix M.

1.1.7.2 Excluded studies

Studies excluded in the full text review are listed in appendix O.

1.1.8 Summary of included economic evidence

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
Cameron et al (2009)								
Partially applicable (appendix M; table 28) with minor limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes mild/ moderate and severe hypoglycaemic events, CVD, nephropathy, gangrene, ketoacidosis, cataract, foot ulcer, neuropathy, depression from hypoglycaemic events **Perspective:** Canadian third-party payer	**Analysis 1**						**Deterministic:** Sensitivity analysis showed that when fear of hypoglycaemia was accounted for ICERs decreased for both analyses, while when differences in HbA1c levels between insulins were ignored, ICERs increased significantly in both analyses. **Probabilistic:** Detemir and Glargine had a 29.2% and 42.5% probability of being cost-effective at a WTP of Can($) 50,000/ QALY
		NPH	40,026[a]	11.034				
		Detemir	42,570[a]	11.045	2,543	0.011	231,195	
		Analysis 2						
		NPH	39,441[a]	11.097				
		Glargine	41,420[a]	11.136	1,979	0.039	50,753	
Dawoud et al (2017)								
Directly applicable (appendix M; table 28) with minor limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model 8.5 – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes severe hypoglycaemic events, CVD, renal complications, eye disease, foot ulcer, neuropathy, and depression **Perspective:** UK National Health Service	**NPH once daily**	38,986	10.95				**Deterministic:** Results remained robust to changes in input parameters and scenarios considered. **Probabilistic:** At a WTP of £20,000/QALY, Detemir (twice daily) had the highest probability of being cost-effective (26%). This increased to 41% at a WTP of £30,000.
		NPH twice daily	39,585	10.97			ext. dom.	
		Glargine 100 IU once daily	40,007	11.04			ext. dom.	
		Detemir once daily	40,097	11.03			dominated	
		Detemir twice daily	40,404	11.09	397	0.05	7,940	
		NPH four times daily	41,968	10.75			dominated	
		Degludec once daily	43,096	10.99			dominated	
Ericcson et al (2012)								
Partially applicable (appendix M; table 28)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness	**Glargine**	1,421	0.261				**Deterministic:** Results were most sensitive to changes in treatment effect of degludec vs
		Degludec	1,492	0.306	71	0.044	1,618	

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
with minor limitations (appendix M; table 29)	(QALYs) associated with hypoglycaemic events within a 1-year time horizon **Diabetes related complications considered:** Severe, non-severe daytime and non-severe nocturnal hypoglycaemic events **Perspective:** Swedish healthcare perspective							glargine for hypoglycaemic events. The scenario of degludec vs NPH resulted in an ICER of SEK 22,736/ QALY **Probabilistic:** Degludec had a 91.2% probability of being cost-effective at a threshold of SEK 500,000/QALY
Evans et al (2015a)								
Partially applicable (appendix M; table 28) with minor limitations (appendix M; table 29)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** Severe, non-severe daytime and non-severe nocturnal hypoglycaemic events **Perspective:** UK National Health Service	**Glargine**	2,112	NR				**Deterministic:** Results were sensitive to hypoglycaemic events rates, rate of SMGB testing, and insulin doses. **Probabilistic:** Degludec had probabilities of 55.98% & 67.89% of being cost-effective at a WTP thresholds of £20,000 & £30,000/ QALY
		Degludec	2,250	NR	138	0.0082	16,895	
Evans et al (2015b)								
Partially applicable (appendix M; table 28) with very serious limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables **Diabetes related complications considered:** Hypoglycaemic events included. Other complications unclear. **Perspective:** UK National Health Service	**Glargine/ Detemir**	822	NR				**Deterministic:** Treatment effect of degludec vs glargine/detemir for HbA1c levels and hypoglycaemic events which had an impact on incremental QALYs **Probabilistic:** NR
		Degludec	1,149	NR	327	NR	Dominant	
Evans et al (2017)								
Partially applicable (appendix M; table 28) with minor limitations (appendix M; table 29)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon.	**Glargine U100**	1,372	NR				**Deterministic:** Results remained robust to changes in input parameters. The scenario of Degludec vs Abasaglar resulted in an ICER £2,027/ QALY and the scenario of using
		Degludec	1,330	NR	-41.23	0.0044	Dominant	

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
	Diabetes related complications considered: Severe and non-severe hypoglycaemic events **Perspective:** UK National Health Service							Glargine U300 resulted in Degludec being dominant. In both these scenarios, only the price of insulins were changed. **Probabilistic:** Degludec had a 65% - 70% probability of being cost-effective at a WTP in excess of £10,000/ QALY
Evans et al (2018)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** Severe, non-severe nocturnal and non-severe daytime hypoglycaemic events **Perspective:** UK National Health Service	**Glargine U100**	1,505	0.7509				**Deterministic:** Results most sensitive to changes in hypoglycaemic event rates. **Probabilistic:** Degludec had a 99.8% probability of being cost-effective at a WTP of £20,000/ QALY
		Degludec	1,527	0.7741	22	0.0232	984	
Grima et al (2007)								
Partially applicable (appendix M; table 28) with very serious limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** includes hypoglycaemic events, CVD, retinopathy, nephropathy, and ketoacidosis **Perspective:** Canadian public payer (ministry of health)	**NPH**	29,465 [a]	10.733				**Deterministic:** Results were most sensitive **to** treatment effects of Glargine vs NPH on HbA1c levels and baseline HbA1c levels. **Probabilistic:** NR
		Glargine	30,280 [a]	10.666	815	0.067	12,166	
Gschwend et al (2009)								
Partially applicable (appendix M; table 28) with very serious limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are	**Belgium**						**Deterministic:** Results were most sensitive to differences in major hypoglycaemic rates in the German context. Variations in time horizons also had a noticeable impact with smaller time horizons failing to capture long-term clinical outcomes and resulted in smaller benefits at
		NPH	107,292 [a]	7.33				
		Detemir	97,778 [a]	7.85	-9,514	0.52	Dominant	
		France						
		NPH	49,293 [a]	7.92				

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
	moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes severe hypoglycaemic events, CVD, renal disease, amputation, vision impairment. **Perspective:** Third party payer perspective in Belgium, France, Germany, Italy and Spain	**Detemir**	49,515 [a]	8.47	221	0.55	402	lower costs. Same patterns were observed in France, Belgium, Italian and Spanish settings (data not shown) **Probabilistic:** Detemir had a 100% probability of being cost-effective at a WTP of €50,000 euros/ QALY in all 5 countries
		Germany						
		NPH	62,234 [a]	6.59				
		Detemir	61,532 [a]	7.04	-702	0.45	Dominant	
		Italy						
		NPH	76,297 [a]	8.39				
		Detemir	77,903 [a]	8.98	1,606	0.58	2,768	
		Spain						
		NPH	42,263 [a]	6.19				
		Detemir	41,718 [a]	6.59	-545	0.4	Dominant	
Haldrup et al (2020)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model 9.0 – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes hypoglycaemic events (severe, non-severe nocturnal, non-severe daytime), CVD, renal, retinopathy, macular edema, cataract, foot ulcer, neuropathy, and depression **Perspective:** Italian healthcare payer	**Others**	200,379 [a]	9.544				**Deterministic:** Results most sensitive to shorter time horizon and treatment effects for HbA1c levels **Probabilistic:** The NMB at a WTP of €30,000 of switching to degludec vs continuing previous basal insulin regimen was 29,710 euros
		Degludec	194,109 [a]	10.325	-6,270	0.781	Dominant	
Hallin et al (2017)								
Partially applicable (appendix M; table 28) with potentially serious	**Approach to analysis:** CORE Diabetes model 9.0 - a lifetime Markov simulation model predicting the progression of diabetes over time	**Others**	NR	NR				**Deterministic:** Results remained robust to changes in input parameters considered. **Probabilistic:** NR
		Degludec	NR	NR	-3,166 [a]	0.54	Dominant	

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
limitations (appendix M; table 29)	using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** includes hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal), CVD, renal, retinopathy, macular edema, cataract, foot ulcer, neuropathy, and depression. **Perspective:** Swedish healthcare sector (direct healthcare costs financed by tax payments and co-payments)							
Lalic et al (2018)								
Partially applicable (appendix M; table 28) with minor limitations (appendix M; table 29)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal) **Perspective:** Serbian healthcare payer	**Glargine U100**	4,757[b]	NR				**Deterministic:** Results most sensitive to changes in hypoglycaemic event rates, insulin dose, and SMGB test used per week. **Probabilistic:** Degludec had a 77.5% probability of being cost-effective at a WTP of RSD 2,048,112/ QALY
		Degludec	5,085 [b]	NR	328	0.0287	11,445	
McEwan et al (2007)								
Partially applicable (appendix M; table 28) with very serious limitations (appendix M; table 29)	**Approach to analysis:** Discrete event simulation model which uses transition functions for the development of five vascular and two glycaemic complications to simulate disease progression in type 1 diabetes patients. The model was based on a simplified version disease progression by Palmer et al[14]. **Diabetes related complications considered:** includes CVDs, renal disease, amputation, vision loss, hypoglycaemic events (severe, nocturnal and symptomatic), and ketoacidosis. **Perspective:** UK National Health Service	**Scenario 1**						**Deterministic:** Results were most sensitive to price of glargine, disutility post hypoglycaemic events, and the cohorts' mean weight. **Probabilistic:** NR
		NPH	8,708	10.84				
		Glargine	9,805	10.97	1,097	0.12	£8,807	
		Scenario 2						
		NPH	8,703	10.84				
		Glargine	9,784	10.97	1,080	0.12	£8,668	
		Scenario 3						
		NPH	8,703	10.84				
		Glargine	9,747	10.99	1,043	0.14	£7,391	
		Scenario 4						
		NPH	8,713	10.85				
		Glargine	10,084	10.99	1,371	0.14	£9,767	

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
		Scenario 5						
		NPH	8,825	10.83				
		Glargine	9,921	11.18	1,096	0.34	£3,189	
Mezquita-Raya et al (2017)								
Partially applicable (appendix M; table 28) with minor limitations (appendix M; table 29)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** hypoglycaemic events (severe, non-severe) **Perspective:** Spanish national health service	**Glargine**	1,889.22 [a]	NR				**Deterministic:** Results most sensitive to changes number of SMGB tests performed **Probabilistic:** Degludec had an 86.42% probability of being cost-effective at a WTP of €30,000/ QALY
		Degludec	1,890.41[a]	NR	1.19	0.0211	56	
Morales et al (2015)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with non-severe hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** non-severe hypoglycaemic events. **Perspective:** Spanish national health service	**Scenario 1**						**Deterministic:** Results were most sensitive to changes in treatment effects of Detemir vs NPH for hypoglycaemic events and cost of detemir. **Probabilistic:** Detemir had a probability of 89.5% of being cost-effective at a WTP of €30,000 / QALY
		NPH	404 [a]	0.843				
		Detemir	607[a]	0.868	203	0.025	8119	
		Scenario 2						
		NPH	438[a]	0.808				
		Detemir	636 [a]	0.839	197	0.031	6369	
		Scenario 3						
		NPH	715[a]	0.525				
		Detemir	868[a]	0.601	153	0.076	2015	
Palmer et al (2004)								
Partially applicable (appendix M; table 28)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting	**NPH**	32, 698	NR				
		Detemir	34,405	NR	1,707	0.09	19,285	

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
with potentially serious limitations (appendix M; table 29)	the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** includes CVDs, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, and amputation **Perspective:** UK National Health Service							**Deterministic:** Results most sensitive to changes in time horizon and when limiting treatment effects to changes in HbA1c levels. **Probabilistic:** Detemir had a 58% probability of being cost-effective at a WTP of £30,000/ QALY
Palmer et al (2007)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** includes CVDs, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, and amputation. **Perspective:** UK National Health Service	**NPH**	NR	NR				**Deterministic:** Results most sensitive to when limiting treatment effects to changes in HbA1c levels. **Probabilistic:** Detemir had a 95% probability of being cost-effective at a WTP of £25,000/ QALY
		Detemir	NR	NR	1,654	0.66	2,500	
Pedersen-Bjergaard et al (2016)								
Partially applicable (appendix M; table 28)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness	**NPH**	1,759 [a]	0.450				**Deterministic:** Results remained robust to changes in input parameters considered.
		Detemir	1,936 [a]	0.517	176	0.067	2,624	

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
with very serious limitations (appendix M; table 29)	(QALYs) associated with hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal) **Perspective:** Danish healthcare payer perspective							**Probabilistic:** NR
Pfohl et al (2012)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** CRC DES model[13,21] – a MS Excel and C++ based model derived from the CORE model. It uses transition functions for the development of two acute (glycaemic) and five long-term (vascular) complications to simulate disease progression in T1D patients. **Diabetes related complications considered:** includes first stroke, myocardial infarction, hypoglycaemic events (sever, non-severe daytime, non-severe nocturnal), ketoacidosis, end-stage renal disease, severe vision loss and amputation **Perspective:** Statutory Health Insurance in Germany	**NPH**	26,946 [a]	10.92				**Deterministic:** Results most sensitive **to** changes in risk factors and treatment effects on HbA1c levels by Glargine vs NPH. **Probabilistic:** Scatterplot shows that Glargine was dominant in 80.4% of iterations.
		Glargine	22,369 [a]	11.31	-4,576	0.397	Dominant	
Pollock et al (2017)								
Partially applicable (appendix M; table 28) with minor limitations (appendix M; table 29)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal) **Perspective:** Danish healthcare payer perspective	**Glargine U100**	2,404 [a]	0.7841				**Deterministic:** Results remained robust to changes in input parameters. Scenario analysis comparing Degludec to Abasaglar by changing input parameters for insulin prices resulted in an ICER of DKK 62,945 (£6,122) / QALY for Degludec **Probabilistic:** Degludec had an 83.3% probability of being cost-effective at a WTP of DKK 250,000/ QALY
		Degludec	2,258 [a]	0.7877	-145	0.0036	Dominant	
Pollock et al (2018)								
Partially applicable (appendix M; table 28)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness	**NPH**	1,241 [a]	0.192				**Deterministic: Results most sensitive** to changes in hypoglycaemic event rates
		Detemir	1,301 [a]	0.291	60	0.099	610	

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
with potentially serious limitations (appendix M; table 29)	(QALYs) associated with minor hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** non-severe hypoglycaemic events **Perspective:** UK National Health Service							**Probabilistic:** Detemir had a 99.9% probability of being cost-effective at a WTP of £10,000/ QALY
Russel-Szymczyk et al (2019)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal) **Perspective:** Bulgarian national insurance fund	**Biosimilar Glargine U100**	5,376[c]	0.557				**Deterministic: Results most sensitive** to changes in hypoglycaemic event rates **Probabilistic:** At a threshold of 39,619 BGN/QALY Degludec had a 60% probability of being cost effective
		Degludec	5,498[c]	0.572	121	0.015	7,878	
Tunis et al (2009)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes severe hypoglycaemic events (severe and non-severe), CVD, renal disease, amputation, vision impairment, foot ulcer, and peripheral neuropathy. **Perspective:** Canadian provincial government	**NPH**	42,161[a]	9.354				**Deterministic:** Results most sensitive to disutility from hypoglycaemic events. **Probabilistic:** Detemir had a 46.2%, 56.1%, % 61.3% probability of being cost-effective at a WTP of Can($) 20,000, 30,000, & 40,000/ QALY respectively
		Detemir	48,955[a]	9.829	6,795	0.475	14304	
Valentine et al (2006)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are	**Analysis 1**						**Deterministic:** Results most sensitive to changes in HbA1c levels for Detemir vs NPH analysis. Detemir vs Glargine analysis was most sensitive to pharmacy acquisition costs. **Probabilistic:** Detemir had probability of 100% and 80% of being cost-effective at a WTP of
		NPH	180,296[a]	7.32				
		Detemir	184,374[a]	8.018	4,078	0.698	5,842[d]	
		Analysis 2						
		Glargine	182,232[a]	7.179				

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
	moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes severe hypoglycaemic events (severe and non-severe), CVDs, amputation, vision impairment, foot ulcer, and peripheral neuropathy. retinopathy, macular edema, vision loss, and cataract **Perspective:** US health care system	**Detemir**	178,570 [a]	7.242	-3,661	0.063	Dominant	US$50,000/ QALY when compared to NPH and Glargine respectively.
Valentine et al (2011)								
Partially applicable (appendix M; table 28) with potentially serious limitations (appendix M; table 29)	**Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered** included CVDs, diabetic retinopathy, macula oedema, cataract, hypoglycaemic events (major and minor), ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation **Perspective:** Swedish healthcare and societal perspective	**NPH**	232,382 [a]	7.82				**Deterministic:** Results most sensitive to treatment effects of Detemir on HbA1c levels and hypoglycaemic events. **Probabilistic:** At willingness to pay thresholds of SEK 200,000, SEK 300,000 and SEK 400,000, the probability of detemir being cost-effective rose to 99.3%, 99.9% and 100.0%, respectively
		Detemir	226,258 [a]	8.35	-6,124	0.53	Dominant	
Valentine et al (2012)								
Partially applicable (appendix M; table 28) with very serious limitations (appendix M; table 28)	**Approach to analysis:** An Excel based model to estimate the number of non-severe hypoglycaemic events experienced by patients with Type 1diabetes and calculate the effect of those events on quality-adjusted life expectancy and medical costs over 1 year of treatment **Diabetes related complications considered:** non-severe hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal) **Perspective:** Healthcare payer perspective in Denmark, Sweden, Finland, and Norway	**NPH**	NR	NR				**Deterministic:** Model input parameters evaluated included treatment effects of Detemir vs NPH, cost of insulin, disutility from hypoglycaemic events. Results remained robust to changes in input parameters with Detemir remaining cost-effective. **Probabilistic:** Detemir had an 86% - 89% probability of being cost-effective at a WTP of €50,000/ QALY
		Detemir	NR	NR	189[e]	0.019	9951	

Applicability & limitations	Other comments	Intervention	Absolute		Incremental			Uncertainty
			Cost (£)	QALYs	Cost (£)	QALYs	ICER (£ / QALY)	
Warren et al (2004)								
Partially applicable (appendix M; table 28) with very serious limitations (appendix M; table 29)	**Approach to analysis:** Model developed to predict the cost and QALYs associated with hypoglycaemic complications over a period of 9 years. Other long-term complications only considered in alternative analysis. **Diabetes related complications considered:** Severe and symptomatic hypoglycaemic events **Perspective:** UK National Health Service	**NPH**	1,738	NR				**Deterministic: Scenario Analysis:** Results most sensitive to scenario analysis where no utility gained was assumed from reduced fear of hypoglycaemic events. **Probabilistic:** NR
		Glargine	2,311[f] – 2,554[f]	NR	573 – 816	NR	3,496 - 4,978	

Abbreviations: CVD, Cardiovascular disease; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; n/a, not applicable; NR, not reported; QALYs, quality-adjusted life years, QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

(a) Converted from the original currency to Great British Pounds (£) using the Purchasing power parities and exchange rates[29] at the year at which costs in original publication was inflated to. See tables 1-27 in appendix M for details.

(b) Converted from Serbian dinars to Great British Pounds (£) using the 2017 Purchasing Power Parities Benchmark results[30] in the Health category. See table 12 in appendix M for details.

(c) Converted from Bulgarian Levs to Great British Pounds (£) using the 2017 Purchasing Power Parities Benchmark results[30] in the Health category. See table 22 in appendix M for details.

(d) Recalculated by dividing incremental costs by incremental QALYs as reported ICERs did not tally.

(e) Converted from Euros to Great British Pounds (£) using the rates attributed to Finland in the Purchasing power parities and exchange rates[29] at the year at which costs in original publication was inflated to. See table 26 in appendix M for details.

(f) Results from 2 alternative analysis using different sources when obtaining input parameters for effectiveness.

1.1.9 Economic model

An original cost-effectiveness model based on the premise of updating the work in the previous guideline was undertaken for this question. A summary is included here, with the full analysis available in the economic model report.

Model structure

The economic analysis was done using the IQVIA CORE Diabetes model (CDM) version 9.5. IQVIA CDM is a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. The model has been previously validated[28] against epidemiological and clinical studies of type 1 diabetes. A more detailed description of IQVIA CDM has been published by Palmer et al (2004). The model allows for transition probabilities and management strategies to be differentiated by type of diabetes. In our analysis, type 1 diabetes data was used where available.

Diabetes progression with the IQVIA CDM is simulated using a series of interlinked, inter-dependent sub-models which simulate the following complications:

- angina
- myocardial infarction
- congestive heart failure
- stroke
- peripheral vascular disease
- diabetic retinopathy
- macular oedema
- cataract
- hypoglycaemia
- ketoacidosis
- lactic acidosis
- nephropathy and end-stage renal disease
- neuropathy
- foot ulcer
- amputation
- non-specific mortality

The Markov sub models listed above use time, state, and diabetes type-dependent probabilities from published sources. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables[29].

The following insulin therapies were compared against each other (based on those regimens for which evidence was identified in the clinical review):

- Insulin Detemir (once daily)
- Insulin Detemir (twice daily)
- Insulin Glargine U100 (once daily)
- Insulin Glargine U300 (once daily)
- Insulin Degludec (once daily)
- NPH (once daily)
- NPH (twice daily)

- Insulin Abasaglar (once daily) – glargine biosimilar
- Insulin Semglee (once daily) – glargine biosimilar

The daily doses (both basal and bolus) for each arm were calculated using mean differences from NMAs of the included RCTs. Daily doses for biosimilars of glargine were assumed to be the same as insulin glargine U100.

Analysis

A cohort of type 1 diabetes patients were defined using patient demographics, racial characteristics, baseline risk factors, and baseline complications to reflect an adult type 1 diabetes population in the UK. The analysis was performed across a lifetime horizon with costs and outcomes discounted at an annual rate of 3.5%. Discounted outcomes and costs were used to calculate the net monetary benefit (NMB) of insulin regiment at a willingness to pay (WTP) per QALY of £20,000 and £30,000. The analysis was undertaken from the perspective of the UK NHS and Personal Social Services.

Treatment effectiveness was characterised using a range of outcomes including reduction in HbA1c levels, severe hypoglycaemic events, non-severe hypoglycaemic events and proportion of nocturnal hypoglycaemic events. These treatment effects were sourced from the NMA as outlined in appendix M.

UK specific sources were identified model inputs relating to costs, utilities, and other management parameters. In cases where UK specific sources were not available, default IQVIA CDM parameters were used. Treatment specific costs were calculated using dosing information from trials, and drug tariff prices obtained by national sources (weighted according to prescription information from the PCA if multiple products were available). Model input parameters used were validated with committee members and explained in more detail in appendix N.

Base case results were looked at across three scenarios, each of which took a different approach when incorporating treatment effects for hypoglycaemic events from the NMA. In scenario 1 all the results from the NMA of severe and all hypoglycaemic events were incorporated, in scenario 2 results of all hypoglycaemic events from the NMA were combined with proportions of severe hypoglycaemic events in RCTs, and in scenario 3 it was assumed that there were no differences in hypoglycaemic events between insulin regimens.

Results

In scenario 1 detemir twice daily was the most cost-effective treatment option in the deterministic analysis (table HE01). This held across both the probabilistic analysis and other deterministic analysis performed sensitivity analysis, except when limiting the time horizon to one year (where the cheapest treatment option of NPH twice daily was the most cost-effective). In scenario 1, glargine U100 once daily was the most cost-effective once daily insulin regimen at a WTP of £20,000. Degludec U100 was the most cost-effective once daily insulin regimen at a WTP of £30,000, except in a scenario where the price of glargine U100 was reduced to that of its cheapest biosimilar (Semglee).

Table HE01: Base-case deterministic cost–utility results (scenario 1)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.54	55,429	175,271	290,621	1	1
NPHx2	17.40	11.40	53,444	174,516	288,496	2	2
GlargU100x1	17.42	11.11	54,934	167,346	278,486	3	4

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Degx1	17.41	11.17	56,650	166,790	278,510	4	3
Detx1	17.41	11.16	57,151	165,949	277,499	5	5
NPHx1	17.35	10.89	57,886	159,994	268,934	6	6
GlargU300x1	17.43	10.77	58,295	157,025	264,685	7	7

(a) Ranked in descending order according to net monetary benefit

Treatment decisions in the base case for scenario 1 broadly held across most subgroups barring an older population and a population with lower baseline levels of HbA1c where NPH twice daily was the most cost-effective at a WTP of £20,000 per QALY. The preference for NPH twice daily was due to a combination of its cheaper price, the shorter life expectancy in older people which resulted in them not experiencing the long-term benefits due to reduced HbA1c levels offered by other insulin regimens for as long a period of time, and the effects of reductions in HbA1c by other insulin regimens being dampened in populations with lower baseline levels of HbA1c.

In scenario 2 detemir twice daily remained the most cost-effective treatment option in the deterministic analysis (table HE02). Glargine U100 once daily was the second most cost-effective across all regimens, and the most cost-effective amongst once daily regimens. Glargine ranked higher in scenario 2 due to differences in severe hypoglycaemic events between glargine U100 once daily and other regiments being smaller when compared to scenario 1 (because the NMA for all hypoglycaemic events found a smaller benefit for detemir versus glargine than the NMA for severe hypoglycaemic events).

Table HE02: Base-case deterministic cost–utility results (scenario 2)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.47	55,795	173,685	288,425	1	1
GlargU100x1	17.42	11.30	53,836	172,144	285,134	2	2
NPHx2	17.40	11.30	54,028	171,972	284,972	3	3
Detx1	17.41	11.34	56,056	170,744	284,144	4	4
Degx1	17.41	11.29	55,920	169,960	282,900	5	5
GlargU300x1	17.43	11.22	55,589	168,791	280,981	6	6
NPHx1	17.35	11.09	56,722	165,098	276,008	7	7

(a) Ranked in descending order according to net monetary benefit

The results in the base case held across both probabilistic and deterministic sensitivity analysis except when limiting the time horizon to one year and in a scenario where the price of glargine U100 was reduced by 39% which resulted in glargine U100 being the most cost-effective treatment strategy at a WTP of £20,000 per QALY. The most cost-effective treatment option in scenario 2 did not change in specific subgroups.

Scenario 3, where no differences in hypoglycaemic events were assumed across insulin regimens, reported results favouring regimens which resulted in the largest decrease in HbA1c levels (table HE03).

Table HE03: Base-case deterministic cost–utility results (scenario 3)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.59	52,592	179,248	295,168	1	1
GlargU300x1	17.43	11.54	54,271	176,429	291,779	2	2
NPHx2	17.40	11.48	53,226	176,354	291,144	3	3
Degx1	17.41	11.53	54,896	175,684	290,974	4	4
Detx2	17.43	11.54	55,429	175,271	290,621	5	5
Detx1	17.41	11.48	55,399	174,241	289,061	6	6
NPHx1	17.35	11.41	55,410	172,810	286,920	7	7

(a) Ranked in descending order according to net monetary benefit

1.1.11 Evidence statements

Pairwise analysis (not summarised using GRADE)

Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. Pairwise data for which GRADE could not be applied is summarised in appendix H.

Glargine U100 vs NPH

1 study identified showed a significant improvement in diabetes-related worries in the glargine U100 arm compared to the NPH arm. The study could not differentiate the following quality of life measures in adults with type 1 diabetes using glargine U100 compared to those using NPH:

- Change in impact
- Change in satisfaction
- General worries

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee identified change in HbA1c and hypoglycaemia, particularly severe and nocturnal hypoglycaemia as critical outcomes. These outcomes were prioritised for network meta-analyses (NMAs). The committee also identified other important outcomes which are listed in the review protocol in appendix A.

1.1.12.2 The quality of the evidence

Overall, 51 studies were included in the review which compared different long-acting insulins and frequencies at which the insulins were given (breakdown of comparisons provided in section 1.1.4). These studies provided sufficient evidence to combine data into a network meta-analysis (NMA) for outcomes of change in HbA1c, all hypoglycaemia as well as severe and nocturnal hypoglycaemia.

Additionally, the studies provided data on important outcomes such as adverse events and change in weight. Evidence on quality of life was also identified for glargine U100 when compared with NPH and glargine U300 when compared with glargine U100. It should also be noted that no evidence was identified for outcomes such as diabetic ketoacidosis, hospital admissions and incidence of cancer.

Results from the NMAs ranged from low to very low quality and results for all other outcomes also ranged in quality. This is because studies were predominantly downgraded for risk of bias due to insufficient information on the randomisation process, open label design and lack of information on the washout period in crossover trials.

Overall, 3 studies were also identified that used regimens where insulin was given more than twice daily, which did not match the review protocol. Two studies compared glargine U100 with NPH four time daily [Porcellati 2000 and Rossetti 2003] and 1 study compared glargine U100 once daily with NPH twice or more daily [Bolli 2009]. Bolli 2009 did report that within the NPH group, 62 participants received NPH twice daily, 10 participants received NPH three times daily and 2 participants received NPH four times daily. These studies were downgraded for indirectness. Additionally, the committee highlighted that NPH four times daily was not used in practice as it was not well tolerated by patients and was not included in the NMAs.

Furthermore, a number of studies were identified which included participants receiving mixed regimens, for example, once or twice daily regimens [Bartley 2008, Zachariah 2011, Home 2005, Heller 2009, Raskin 2000, Renard 2011, Rosenstock 2009 and Ratner 2000]. These studies did not provide data separately for the two subgroups. While these studies were not downgraded for indirectness, the committee noted that, these studies did highlight some significant results but were not useful in the development of recommendations.

Additionally, long-acting insulins used in combination with short-acting or rapid acting insulins were included in this review. Bolus insulins used in the studies included aspart, lispro, regular human insulin and glulisine. In the majority of the studies, the same bolus insulins were used in both arms, but some studies did not state the bolus insulin that was utilised. For example, studies comparing glargine U100 with Glargine U300, simply stated that long-acting insulins were given alongside mealtime insulin or that participants continued their existing mealtime regimen [Bergenstal 2017, EDITION 4 trial, EDITION 4 JP1 trial, Jinnouchi 2015 and Pettus 2019]. As it was unclear if both arms in these studies were equal in terms of the mealtime insulin, the studies were also downgraded for indirectness.

It was also noted that studies in the same comparison utilised different bolus insulins. For example, studies comparing glargine U100 with NPH used unmodified human insulin, regular human insulin and lispro. However, the committee highlighted that use of different bolus insulins should not have an impact on the overall estimate.

Two further studies were identified [Iga 2017 and Onda 2017] which compared degludec with glargine but did not specify the concentration of the insulins. These studies were also downgraded for indirectness and the committee further noted that these studies were not useful in the development of recommendations. Therefore, these studies were not included in the NMA.

While a minimum follow-up period was not specified in the review protocol, 3 studies were identified where participants were followed up for less than 4 weeks [Heise 2012, Jinnouchi 2015 and Heise 2017]. The committee noted that a follow-up period of less than 4 weeks was too short to evaluate the effectiveness of long-acting insulins. These studies were not downgraded for indirectness but were excluded from the NMA analyses. This meant that direct evidence comparing degludec U200 and glargine U300 was not included in the NMAs (for further information on the studies included in the NMAs, see appendix K). While other studies contributed to evidence on glargine U300, degludec U200 was not a treatment option in the NMAs.

It was also identified that several studies were funded by the pharmaceutical industry. For example, Pieber 2007, which was the main study comparing detemir twice daily with glargine U100 once daily, was an industry funded trial, with several competing interests. The study also identified that there were four times as many severe hypoglycaemic events in the

glargine U100 arm compared to detemir. The committee highlighted that in practice, such a high number of hypoglycaemic events are not seen in people using glargine U100.

The committee further highlighted that along with being industry funded, these trials often include people who are highly motivated and who are provided extensive support. Additionally, the committee noted that in practice, type of insulin therapy given to a patient is governed by comorbidities such as age, impaired renal function, diet and hypoglycaemic unawareness. Using Pieber 2007 as an example, the study excluded people with significant medical problems, including impaired renal and hepatic function as well as people with hypoglycaemic unawareness. RCTs were considered gold standard for this review, but the committee did note that the studies did not replicate real-life clinical scenarios. These studies were not downgraded but potential biases associated with RCT evidence were acknowledged.

Moreover, 5 studies [Blevins 2015, Blevins 2018, Perez-Nieves 2018, Home 2018 and Karanova 2020] were identified which compared biosimilars to originator glargine U100. No studies were identified which compared biosimilars to other long-acting insulins. The studies could not differentiate between biosimilars and originator glargine in outcomes such as change in HbA1c, participants achieving HbA1c target and hypoglycaemia.

As these studies only compared the biosimilars to originator glargine, the committee were unable to form specific recommendations, due to the NICE position statement on biosimilars stating that once they are licensed, they are assumed in our processes to be equally effective. Therefore, the committee recommended that when initiating insulin for which a biosimilar is available, then the product with the lowest acquisition cost should be used. The committee also highlighted that guidance produced by the MHRA on minimising the risk of medication error with insulins can be useful for healthcare professionals when starting treatment with a biosimilar.

The committee also discussed whether making research recommendations around biosimilars was relevant but agreed there are already established processes and evidence requirements for licensing biosimilars, and therefore making such a recommendation was not necessary.

Evidence from the NMAs was prioritised when forming recommendations. However, while the evidence demonstrated some clinically significant results, uncertainty with the evidence was also identified. The NMA for change in HbA1c could not differentiate between the different long-acting insulins. However, while a meaningful difference was not identified, the evidence did demonstrate equivalence between the long-acting insulins. Additionally, no significant difference was identified between the different treatment options and the baseline comparator (detemir twice daily). Rank probabilities further highlighted the uncertainty of this evidence.

The committee noted that while HbA1c is useful, due to large variabilities in glucose values, an HbA1c test is not always a reliable measure of glycaemic control. The committee further stated that following the introduction of continuous glucose monitoring into clinical practice, time in target glucose range is clinically seen as a more reliable marker of glycaemic control than HbA1c.

Additionally, the NMA for all hypoglycaemic events could not differentiate between the different long-acting insulins and did not demonstrate equivalence between the different treatment options. The credible intervals were also wide which further demonstrated uncertainty in the evidence. This uncertainty in the evidence was also reflected in the rank probabilities. Due to this uncertainty this evidence was downgraded for very serious imprecision.

The NMA on severe and nocturnal hypoglycaemia did identify some meaningful differences. The NMA for serious hypoglycaemia did identify a meaningful difference between detemir

twice daily and NPH once/twice daily as well as detemir once/twice daily and NPH once/twice daily. However, the credible intervals were wide which suggested uncertainty in the evidence. Furthermore, the rank probabilities did identify detemir twice daily as a better treatment option compared to NPH once/twice daily, but this evidence also highlighted the uncertainty in the evidence. Due to this uncertainty, the evidence was downgraded for very serious imprecision.

Also, the NMA on nocturnal hypoglycaemia identified a significant difference between detemir twice daily and degludec U100 as well as between degludec U100 and glargine U100, detemir once daily and NPH once daily. Rank probabilities also identified degludec U100 as one of the better treatment options compared to NPH once daily. The evidence also identified glargine twice daily as one of the better treatment options. However, the direct evidence from a single study and the indirect evidence identified no significant difference between glargine twice daily and other treatment options.

For all other treatment options, the credible intervals were wide and crossed the line of no effect which meant significance was not reached. Due to this uncertainty, the evidence was downgraded for serious imprecision. The committee further noted that while there was some uncertainty around the evidence, this evidence did allow potential treatment options to be identified.

1.1.12.3 Benefits and harms

Hypoglycaemia, particularly severe and nocturnal hypoglycaemia are major concerns in people with type 1 diabetes. If left untreated, severe hypoglycaemic events can be life threatening and can have a major impact on quality of life. NMA results showed that there were fewer severe/major hypoglycaemic events with detemir twice daily and detemir once or twice daily compared to NPH once or twice daily.

This evidence identified that detemir twice daily significantly reduced the number of severe and nocturnal hypoglycaemic events when compared to other long-acting insulins. This demonstrated that detemir twice daily can play a role in the treatment pathway. The committee further stated that while practice varies across the country, some centres do use detemir twice daily in people newly diagnosed with type 1 diabetes. Based on the evidence and their clinical expertise, the committee retained the 2015 recommendations which state that twice daily insulin detemir should be offered as basal insulin therapy for adults with type 1 diabetes. The committee also noted that the use of twice daily regimen can give some people flexibility around their lifestyle, for example exercising and alcohol consumption.

The committee also noted that hypoglycaemia is a common side effect of insulin therapy. This is a particular cause of concern especially if people exhibit nocturnal hypoglycaemia as symptoms are only realised once waking from an episode. Evidence from the NMA highlighted that there was a lower proportion of nocturnal hypoglycaemic events with degludec U100 once daily when compared to glargine U100, detemir once daily and NPH once daily.

Based on the evidence, the committee highlighted that degludec U100 can be considered as a useful alternative for people exhibiting nocturnal hypoglycaemia even after using detemir twice daily as first line treatment. Compared to long-acting insulins, degludec is an ultra-long-acting insulin and has a duration of more than 42 hours. Therefore, the committee expanded existing recommendations to state that degludec U100 can be considered as an alternative basal insulin therapy it there is a particular concern about nocturnal hypoglycaemia.

Current recommendations on insulin regimens state that multiple daily injection basal-bolus insulin regimens should be offered as a choice for all adults with type 1 diabetes. This means that people with type 1 diabetes must take a number of injections throughout the day, along with self-monitoring, which may be done through finger pricking. While multiple daily injections can help people achieve their treatment goals, one of the side effects of insulin

therapy is injection site reactions. Several studies were identified that reported evidence on injection site reactions, but the studies did not identify a clinically significant difference between the different long-acting insulins.

Evidence on quality of life was limited and 1 study [Witthaus 2001] could not differentiate between glargine U100 once daily and NPH once or more than once daily in outcomes such as change in general wellbeing and change in anxiety. However, the committee noted that multiple daily injections also have implications on quality of life and stressed that clinical evidence should be assessed alongside patient perspective. Regimens such as NPH four times daily were ruled out by the committee as this was not reflective of practice, would not be well tolerated by patients and could significantly impact quality of life.

The committee noted that detemir twice daily might not be tolerated, preferred or be practical for everyone, which means that an alternative once-daily regimen should be considered. The committee highlighted that glargine U100 once daily is commonly used in practice and evidence identified in the review could not differentiate between detemir twice daily and glargine U100 in outcomes such as severe/major and nocturnal hypoglycaemia. Based on this understanding, the committee expanded on current recommendations to state that once daily insulin glargine U100 can be considered as an alternative basal insulin therapy to twice-daily insulin detemir if insulin detemir is not tolerated or the person has a strong preference for once-daily injections.

1.1.12.4 Cost effectiveness and resource use

The committee agreed that, both due to the differences in costs between the different insulins, and the evidence for differences in hypoglycaemic events rates (which result in both costs and quality of life losses) cost-effectiveness evidence was important to inform their decision-making. They also noted that none of the published studies was sufficient for this, both due to the publication of more recent RCTs, and the fact that most of these analyses only compared a subset of the relevant insulin treatment options, and therefore a new analysis was necessary. Evidence from this economic analysis was considered by the committee when making recommendations for this guideline.

Given the structure of our economic analysis, which was performed in the IQVIA Core Diabetes Model, and the model input parameters used, it was evident that treatment decisions are likely to be driven by treatment effects on HbA1c levels and hypoglycaemic events, and the treatment costs of each insulin regimen.

Given the results from the NMA where changes in HbA1c levels were similar across insulin regimens, treatment effects on HbA1c levels were unlikely to drive treatment decisions (compared to the larger differences in the mean estimates for both costs and hypoglycaemic events).

Results from the NMA did show large differences in the point estimates of severe and all hypoglycaemic event rates. However large amounts of uncertainty around the data meant that differences were not significant. It is with this uncertainty in mind that three scenarios were considered in our analysis; one where all NMA data on severe and all hypoglycaemic events were considered (scenario 1), one where data from the NMA on only all hypoglycaemic events was considered (scenario 2), and one where no data from the NMAs on hypoglycaemic events were considered (scenario 3). Particular attention was given to scenarios 1 and 2 in our base case analysis (full details of these scenarios are given in the economic modelling report).

Scenario 1 incorporated information from all available NMA data (including the NMAs on severe hypoglycaemic events and all hypoglycaemic events) and reported that the two twice daily regimens, detemir twice daily and NPH twice daily, ranked first and second in terms of cost-effectiveness in both the deterministic and probabilistic analysis. Amongst the once daily regimens glargine U100 was the most cost-effective option at a WTP of £20,000 per QALY,

with this changing to degludec U100 once daily at a WTP of £30,000 per QALY. In a probabilistic analysis considering once daily insulin regimens, glargine U100 had a 52.5% and 49% probability of being cost-effective at a WTP of £20,000 and £30,000 per QALY respectively when compared to degludec U100. Before the results for the NMAs were available, this represented the committee's preferred scenario, as it made use of the full available data from the included RCTs. However, after seeing the results from the NMAs, they noted it was also the scenario containing the highest levels of uncertainty, due to the lower rate of severe hypoglycaemic events compared to all hypoglycaemic events, and therefore agreed it was necessary to also give significant weight to the results of scenario 2, due to the lower associated parameter uncertainty in that analysis.

Scenario 2 excluded results from the NMA of severe hypoglycaemic events due to the large levels of uncertainty surrounding point estimates (instead assuming a fixed proportion of hypoglycaemic events are severe, and applying that to the data from the NMA on all hypoglycaemic events), and reported that detemir twice daily was still the most cost-effective treatment strategy in both the deterministic and probabilistic analysis. However, glargine U100 once daily ranked second in this scenario. The improved cost-effectiveness of glargine U100 once daily was due to the exclusion of results of the NMA of severe hypoglycaemic events, which reported higher severe hypoglycaemic event rates for glargine U100 once daily (with high levels of uncertainty) which was driven by data from a single trial, Pieber et al (2007), comparing detemir twice daily vs glargine u100 once daily, reporting 4 severe hypoglycaemic events in the detemir twice daily arm and 15 in the glargine u100 once daily arm (see the section above on the quality of the evidence for a more detailed discussion on this study).

A third scenario assuming no differences in hypoglycaemic event rates between insulin regimens was also conducted. However, this scenario was given lower weight in decision-making as the committee agreed both that differences between insulins in terms of hypoglycaemic events would be expected, and that these would often be the key factor considered when deciding on an insulin for a particular individual.

Given the importance of treatment costs on the analysis, priority was given to capture all relevant costs which were likely to differ by insulin regimens. This included 2 additional NMAs being performed to capture the daily basal and bolus insulin doses for each regimen, needle costs when they differed by regimen, and drug costs calculated by considering all available products and weighting these costs using PCA data. Two additional sensitivity analysis was performed to test the robustness of the model relating to these model inputs; one assuming a daily basal and bolus dose of 24 units across all insulin regimes (results showing no change in the treatment decision when compared to the base case) and a scenario where the price of glargine U100 was reduced to account for biosimilars in the market.

When the price of glargine U100 was reduced to that of biosimilar Semglee, the only change in treatment decision happened in scenario 1 where now glargine U100 once daily was the most cost-effective once daily insulin regimen at both a WTP of £20,000 and £30,000 per QALY. However, the differences in hypoglycaemic event rates between glargine U100 once daily and detemir twice daily were too large for a reduction in the price of glargine to change the treatment decision relating to the most cost-effective overall treatment strategy. In scenario 2, our sensitivity analysis showed the price of a 5x3ml pack of a biosimilar for glargine U100 would have to be at least 39% cheaper than the current glargine U100 price for it to be cost-effective at a WTP of £20,000 per QALY (Semglee, the cheapest biosimilar in the market has a price reduction of around 21% at present).

Other sensitivity analysis performed in our analysis included reducing the discount rate to 1.5%, reducing the time horizon to one year, reducing the baseline quality of life of patients, and increasing the proportion of nocturnal hypoglycaemic events. Of these only limiting the time horizon to one year brought a change in the treatment decision across the three

scenarios when compared to the base case, reporting NPH twice daily as the most cost-effective treatment strategy as expected, due to the lower treatment cost of NPH twice daily and the fact that the long-term benefits of other regimens, especially those associated with reductions in HbA1c levels, were not fully captured within a one-year time horizon.

Treatment decisions broadly held across most subgroups barring one in older people and one with a population with lower baseline levels of HbA1c where, in scenario 1, NPH twice daily was the most cost-effective at a WTP of £20,000 per QALY. The preference for NPH twice daily was due to a combination of its cheaper price, and the shortened life expectancy in the older population which resulted in them not experiencing the long-term benefits due to reduced HbA1c levels offered by other insulin regimens for as long a period of time, and the effects of reductions in HbA1c by other insulin regimens being dampened in populations with lower levels of baseline HbA1c. However more information was needed to make recommendations specific to subgroups as subgroups were only accounted for by their specific baseline characteristics (there was no evidence on differences in treatment efficacy between these subgroups).

The committee agreed there was clear evidence for detemir twice daily being the most cost-effective treatment regimen on average across the type 1 diabetes population (it was the most cost-effective consistently in both scenario 1 and scenario 2). The committee therefore agreed it was appropriate to offer this as the first-line insulin therapy of choice unless there were specific individual reasons to make a different choice.

The committee then discussed what some of these individual reasons might be. First, they noted there may be individuals who are either not able to tolerate insulin detemir, or for whom a once daily regimen is necessary (either because of strong preferences on behalf of the individual or circumstances that make twice daily injection not practical). Glargine U100 was considered a viable option when considering once daily regimens, with results showing that it was the most cost-effective treatment option across once daily regimens when incorporating all available information on hypoglycaemic events from the NMA (scenario 1) at a WTP of £20,000 per QALY, and at both a WTP of £20,000 and £30,000 per QALY when incorporating only NMA results for all hypoglycaemic events. Additionally, when the price reductions for glargine biosimilars were considered, glargine U100 was felt to be clearly the most cost-effective only daily insulin and was therefore recommended as the appropriate alternative in these cases. The committee noted it was appropriate when starting a new prescription for an insulin where a biosimilar is available to use the one with the lowest cost. They also noted that people not on this cheapest biosimilar for their appropriate insulin should be offered the chance to switch, but this needed to be part of a shared decision with the person, and not something enforced on them.

The committee considered whether there were circumstances in which twice daily NPH insulin was an appropriate insulin to recommend, and they noted that in scenario 1 this was the second most cost-effective option, after twice daily insulin detemir. However, they noted that the number of people who would not be able to tolerate insulin detemir but would still be able to have twice daily injections would be small, and that insulin glargine was more cost-effective than NPH insulin in scenario 2 (the scenario in which more data were available). As a result the committee did not feel making an uncertain recommendation for NPH in this small sub-population would be useful, and therefore agreed it was best to leave insulin glargine as the option for people unable to tolerate insulin detemir.

They also noted that NPH insulin came out as the most cost-effective option for the older age cohort (modelling a population with an average starting age of 62). This is because this population has less time to accrue the benefits of more effective insulin regimens, and therefore the lower cost of NPH insulin becomes more important. However, the committee were not condiment to make this as a recommendation for two reasons. First, there was no clinical evidence available for this subpopulation, and therefore the modelling relied on assuming the comparative clinical effectiveness of insulins is the same in older people, which

the committee felt was plausible, but in the absence of evidence felt uncomfortable making sperate recommendations based on this assumption. Secondly, the committee noted that few people would be initiating insulin therapy at age 62 – the large majority of these people will be on established therapy, and they agreed it would be inappropriate for someone to be switched away from a treatment that is working for them, simply as a result of their age.

The committee also note there was specific evidence that degludec U100 was beneficial for decreasing the proportion of nocturnal hypoglycaemia. Whilst the cost-effectiveness evidence demonstrated this effect was not sufficient to make degludec cost-effective across the whole population, the committee agreed there would be a subset of people, in whom nocturnal hypoglycaemia was a particular concern, where it would be appropriate to consider insulin degludec.

Finally, the committee noted that for people who required help administering their insulin injections, once daily regimens would often be preferable, as it is often impractical for either formal or informal carers to be able to assist with injections twice a day. In these circumstances, the committee agreed that a number of once daily insulins may be appropriate, depending on the circumstances, but noted that insulin degludec may have some advantages in this population, as the longer duration of treatment effect means there is more flexibility in when during the day the insulin is delivered, as opposed to basal insulins with less than 24-hour coverage that may result in periods of no insulin coverage.

The impact on quality of life from different dosing regimens (flexible, once-daily, twice-daily etc.) was not included in the model. The committee initially agreed this was an important issue to address, under the assumption there would likely be a quality of life benefit associated with needing fewer injections, and therefore a specific search was made for papers providing data on this issue. A study by Evans et al has reported findings on the impact of flexible dosing and multiple injection insulin regimens on quality of life, and did include estimates from people with both type 1 and type 2 diabetes. However, the results were not reported by type of diabetes. The committee believed the impact on quality of life from multiple injections and flexible dosing regimens are likely to differ between type 1 and type 2 patients due to the younger average age of type 1 patients, and the difference between the conditions (such as comorbidities, the number of injections needed per day and other medicines being taken). Hence this was not incorporated in our analysis. The committee also noted this study did not consider whether any potential quality of life differences would persist permanently, or whether there would be adaptation effects (meaning the quality of life associated with the different options converged over time as people became used to the regimen they were using). They noted this would also be a relevant factor to consider in any future quality of life studies conducted.

1.1.12.5 Other factors the committee took into account

Treatment goals for people with type 1 diabetes can include meeting their HbA1c targets, spending more time in target glucose range and minimising the number of hypoglycaemic episodes. Some people may find that their existing insulin regimens help them to meet these targets. They also may prefer to continue using their existing insulin regimens which they are familiar with, rather than switching to a new regimen. Based on this understanding, the committee amended the current recommendation to state that the insulin regimen should help meet their agreed treatment goals such as their HbA1c and time in target glucose range targets, as well as minimising hypoglycaemia.

Furthermore, the committee identified older adults (aged 65 and above), people with increased frailty and people who require assistance for injections due to physical disability, mental- health related or learning disability as key subgroups. No evidence on basal insulin therapy was identified in these groups. The committee highlighted that recommendations in these populations were necessary as these groups may be more prone to hypoglycaemia, have fewer warning signs of hypoglycaemia and be less able to take action at onset of

hypoglycaemia. In addition, the consequences of an event could be more severe. For example, older adults and people with increased frailty may suffer a fall because of a hypoglycaemic event, which could lead to fractures and more readily result in hospital admissions.

The committee further noted that these groups may be reliant on district nurses or a carer to administer injections, and administration of twice daily regimens may be challenging and impractical. The committee stated that flexibility of timing was required in this group, and that once daily regimens may be preferred. Flexible insulins, such as degludec U100 and glargine U300, that have a long duration of action may be useful as they give more flexibility in when the dose should be administered. Based on their clinical knowledge, the committee expanded on current recommendations to state that once-daily insulin such as degludec U100 can be considered as an alternative basal insulin therapy to twice-daily insulin detemir for people who need help from a carer or healthcare professional to administer injections.

It was also noted that healthcare professionals should refer to NHS Improvement's patient safety alert severe harm and death due to withdrawing insulin from pen devices. The report highlights that organisations should warn staff that extracting insulin from pen devices or cartridges is dangerous and should not happen. Additionally, to ensure insulin is given safely, staff and patients who use pen devices should be provided with safety needles and access to equipment capable of safely removing and disposing of used insulin pen needles.

As mentioned previously, the committee developed a recommendation which allows some flexibility on the use of biosimilars when initiating treatment. However, it was highlighted that people may already be using an insulin for which a biosimilar is available. Switching over to the biosimilar would be cost saving, however it was important to take patient preference into consideration. People may be reluctant to switch if they are comfortable with the existing therapy and if it is helping them meet their treatment goals.

The committee noted the use of biosimilars could still be explored through shared decision making. Therefore, the committee recommended that when people are already using an insulin for which a lower cost biosimilar is available, discuss the possibility of switching to the biosimilar and to make a shared decision with the person after discussing their preferences. Any concerns the person has about switching from their existing regimen should also be taken into consideration. The committee also agreed that switching to the biosimilar should be carefully planned, taking into consideration the dose switching protocols and monitoring. Additionally, no differences were found in rates of adverse events between any of the different glargine U100 preparations in the included RCTs and the summary of product characteristics (SPC) of different glargine U100 preparations gave the same advice on potential side effects. It was further agreed that healthcare professionals should also refer to the SPC when considering switching to biosimilars.

People with renal impairment were identified as a key subgroup by the committee. They highlighted that while renal impairment does not govern the type of insulin used but it does affect the dose of insulin used. However, no studies were identified which included evidence on this group. The committee further stated that renal impairment should be taken into consideration along with other comorbidities such as age, frailty and hypoglycaemic unawareness when considering basal insulin regimens.

The committee also noted that some people may struggle with adhering to their insulin regimen which can result in them developing diabetic ketoacidosis (DKA). Based on this understanding, the committee stated that DKA and adherence should also be taken into account when considering basal insulin regimens.

It was also highlighted that other basal insulin regimens may be considered if insulins recommended by the committee do not help people meet their target goals. Therefore, the committee retained the 2015 recommendation but further expanded it to state that other basal insulin regimen can be considered, only if regimens in recommendations 1.7.3 and

1.7.4 do not help meet the agreed treatment goals. When choosing an alternative insulin regimen, take account of the person's preferences, comorbidities, risk of hypoglycaemia and the acquisition cost. Additionally, to support pharmacovigilance and patient safety, the committee also recommended that insulins should be prescribed by brand name.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.3- 1.7.8

1.1.14 References – included studies

1.1.14.1 Effectiveness

Ashwell, S G; Gebbie, J; Home, P D (2006) Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. Diabetic medicine: a journal of the British Diabetic Association 23(8): 879-86

Bartley, P C, Bogoev, M, Larsen, J et al. (2008) Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabetic medicine: a journal of the British Diabetic Association 25(4): 442-9

Bergenstal, Richard M, Bailey, Timothy S, Rodbard, David et al. (2017) Comparison of Insulin Glargine 300 Units/mL and 100 Units/mL in Adults With Type 1 Diabetes: Continuous Glucose Monitoring Profiles and Variability Using Morning or Evening Injections. Diabetes care 40(4): 554-560

Birkeland, Kare I, Home, Philip D, Wendisch, Ulrich et al. (2011) Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes care 34(3): 661-5

Blevins, T C, Dahl, D, Rosenstock, J et al. (2015) Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus R) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. Diabetes, obesity & metabolism 17(8): 726-33

Blevins, Thomas C, Barve, Abhijit, Sun, Bin et al. (2018) Efficacy and safety of MYL-1501D vs insulin glargine in patients with type 1 diabetes after 52 weeks: Results of the INSTRIDE 1 phase III study. Diabetes, obesity & metabolism 20(8): 1944-1950

Bode, B W, Buse, J B, Fisher, M et al. (2013) Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN(R) Basal-Bolus Type 1): 2-year results of a randomized clinical trial. Diabetic medicine: a journal of the British Diabetic Association 30(11): 1293-7

Bolli, G B, Songini, M, Trovati, M et al. (2009) Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with Type 1 diabetes. Nutrition, metabolism, and cardiovascular diseases: NMCD 19(8): 571-9

Chatterjee, S, Jarvis-Kay, J, Rengarajan, T et al. (2007) Glargine versus NPH insulin: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes--the glargine and aspart study (GLASS) a randomised cross-over study. Diabetes research and clinical practice 77(2): 215-22

Davies, M J, Gross, J L, Ono, Y et al. (2014) Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week

randomized, open-label, treat-to-target non-inferiority trial. Diabetes, obesity & metabolism 16(10): 922-30

De Leeuw, I, Vague, P, Selam, J-L et al. (2005) Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes, obesity & metabolism 7(1): 73-82

DeLozier, A.M., Ilag, L.L., Perez-Nieves, M. et al. (2018) Patient-reported outcome measures in phase III trials of LY2963016 insulin glargine and reference insulin glargine products: ELEMENT 1 and ELEMENT 2. GaBI Journal 7(2): 6

Fulcher, G R; Gilbert, R E; Yue, D K (2005) Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. Internal medicine journal 35(9): 536-42

Heise, T, Hermanski, L, Nosek, L et al. (2012) Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes, obesity & metabolism 14(9): 859-64

Heise, Tim, Norskov, Marianne, Nosek, Leszek et al. (2017) Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. Diabetes, obesity & metabolism 19(7): 1032-1039

Heller, Simon, Buse, John, Fisher, Miles et al. (2012) Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet (London, England) 379(9825): 1489-97

Heller, Simon; Koenen, Christoph; Bode, Bruce (2009) Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clinical therapeutics 31(10): 2086-97

Hermansen, K, Madsbad, S, Perrild, H et al. (2001) Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes care 24(2): 296-301

Home, P D, Meneghini, L, Wendisch, U et al. (2012) Improved health status with insulin degludec compared with insulin glargine in people with type 1 diabetes. Diabetic medicine: a journal of the British Diabetic Association 29(6): 716-20

Home, P D, Rosskamp, R, Forjanic-Klapproth, J et al. (2005) A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes. Diabetes/metabolism research and reviews 21(6): 545-53

Home, Philip D, Bergenstal, Richard M, Bolli, Geremia B et al. (2015) New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). Diabetes care 38(12): 2217-25

Home, Philip D, Bergenstal, Richard M, Bolli, Geremia B et al. (2018) Glycaemic control and hypoglycaemia during 12 months of randomized treatment with insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 1 diabetes (EDITION 4). Diabetes, obesity & metabolism 20(1): 121-128

Home, Philip D, Lam, Raymond L H, Carofano, Wendy L et al. (2018) Efficacy and safety of MK-1293 insulin glargine compared with originator insulin glargine (Lantus) in type 1 diabetes: A randomized, open-label clinical trial. Diabetes, obesity & metabolism 20(9): 2220-2228

Home, Philip, Bartley, Paul, Russell-Jones, David et al. (2004) Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes care 27(5): 1081-7

Iga, R., Uchino, H., Kanazawa, K. et al. (2017) Glycemic Variability in Type 1 Diabetes Compared with Degludec and Glargine on the Morning Injection: An Open-label Randomized Controlled Trial. Diabetes Therapy 8(4): 783-792

Iwamoto, Y., Clauson, P., Nishida, T. et al. (2013) Insulin degludec in Japanese patients with type 1 diabetes mellitus: A randomized controlled trial. Journal of Diabetes Investigation 4(1): 62-68

Jinnouchi, H., Koyama, M., Amano, A. et al. (2015) Continuous Glucose Monitoring During Basal-Bolus Therapy Using Insulin Glargine 300 U mL-1 and Glargine 100 U mL-1 in Japanese People with Type 1 Diabetes Mellitus: A Crossover Pilot Study. Diabetes Therapy 6(2): 143-152

Karonova, T.L., Mosikian, A.A., Mayorov, A.Y. et al. (2020) Safety and efficacy of GP40061 compared with originator insulin glargine (Lantus): A randomized open-label clinical trial. Journal of Comparative Effectiveness Research 9(4): 263-273

Kolendorf, K, Ross, G P, Pavlic-Renar, I et al. (2006) Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association 23(7): 729-35

Lane, Wendy, Bailey, Timothy S, Gerety, Gregg et al. (2017) Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA 318(1): 33-44

Le Floch, Jean-Pierre, Levy, Marc, Mosnier-Pudar, Helen et al. (2009) Comparison of once- versus twice-daily administration of insulin detemir, used with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treat-to-target trial (ADAPT). Diabetes care 32(1): 32-7

Mathieu, Chantal, Hollander, Priscilla, Miranda-Palma, Bresta et al. (2013) Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. The Journal of clinical endocrinology and metabolism 98(3): 1154-62

Matsuhisa, M, Koyama, M, Cheng, X et al. (2016) New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). Diabetes, obesity & metabolism 18(4): 375-83

Matsuhisa, Munehide, Koyama, Masayoshi, Cheng, Xi et al. (2016) Sustained glycaemic control and less nocturnal hypoglycaemia with insulin glargine 300U/mL compared with glargine 100U/mL in Japanese adults with type 1 diabetes (EDITION JP 1 randomised 12-month trial including 6-month extension). Diabetes research and clinical practice 122: 133-140

Onda, Yoshiko, Nishimura, Rimei, Ando, Kiyotaka et al. (2016) Comparison of glycemic variability in Japanese patients with type 1 diabetes receiving insulin degludec versus insulin glargine using continuous glucose monitoring: A randomized, cross-over, pilot study. Diabetes research and clinical practice 120: 149-55

Pettus, J., Gill, J., Paranjape, S. et al. (2019) Efficacy and safety of a morning injection of insulin glargine 300 units/mL versus insulin glargine 100 units/mL in adult patients with type 1

diabetes: A multicentre, randomized controlled trial using continuous glucose monitoring. Diabetes, Obesity and Metabolism 21(8): 1906-1913

Pieber, T R, Draeger, E, Kristensen, A et al. (2005) Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabetic medicine: a journal of the British Diabetic Association 22(7): 850-7

Pieber, T R, Treichel, H-C, Hompesch, B et al. (2007) Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. Diabetic medicine : a journal of the British Diabetic Association 24(6): 635-42

Pieber, T.R.; Eugene-Jolchine, I.; Derobert, E. (2000) Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. Diabetes Care 23(2): 157-162

Porcellati, F, Rossetti, P, Pampanelli, S et al. (2004) Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. Diabetic medicine : a journal of the British Diabetic Association 21(11): 1213-20

Raskin, P, Klaff, L, Bergenstal, R et al. (2000) A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes care 23(11): 1666-71

Ratner, R E, Hirsch, I B, Neifing, J L et al. (2000) Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes care 23(5): 639-43

Renard, Eric, Dubois-Laforgue, Daniele, Guerci, Bruno et al. (2011) Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability in type 1 diabetes patients: a multicenter, randomized, crossover study. Diabetes technology & therapeutics 13(12): 1213-8

Rosenstock, J, Park, G, Zimmerman, J et al. (2000) Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. Diabetes care 23(8): 1137-42

Rossetti, Paolo, Pampanelli, Simone, Fanelli, Carmine et al. (2003) Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. Diabetes care 26(5): 1490-6

Russell-Jones, David, Simpson, Richard, Hylleberg, Birgitte et al. (2004) Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clinical therapeutics 26(5): 724-36

Standl, Eberhard; Lang, Hanne; Roberts, Anthony (2004) The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes technology & therapeutics 6(5): 579-88

Vague, Philippe, Selam, Jean-Louis, Skeie, Svein et al. (2003) Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes care 26(3): 590-6

van Golen, Larissa W, IJzerman, Richard G, Huisman, Marc C et al. (2013) Cerebral blood flow and glucose metabolism in appetite-related brain regions in type 1 diabetic patients after treatment with insulin detemir and NPH insulin: a randomized controlled crossover trial. Diabetes care 36(12): 4050-6

Witthaus, E; Stewart, J; Bradley, C (2001) Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes. Diabetic medicine: a journal of the British Diabetic Association 18(8): 619-25

Zachariah, Sunil, Sheldon, Ben, Shojaee-Moradie, Fariba et al. (2011) Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes care 34(7): 1487-91

1.1.14.2 Economic

Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. C Can Med Assoc J. 2009;180(4):400-407. http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22009100602/frame.html

Dawoud D, Fenu E, Higgins B, Wonderling D, Amiel SA. Basal Insulin Regimens for Adults with Type 1 Diabetes Mellitus: A Cost-Utility Analysis. Value Heal. 2017;20(10):1279-1287. doi:10.1016/j.jval.2017.05.021

Ericsson Å, Pollock RF, Hunt B, Valentine WJ. Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. J Med Econ. 2013;16(12):1442-1452. doi:10.3111/13696998.2013.852099

Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with type 1 diabetes mellitus in the UK. J Med Econ. 2015a;18(1):56-68. doi:10.3111/13696998.2014.971160

Evans M, McEwan P, Foos V. Insulin degludec early clinical experience: Does the promise from the clinical trials translate into clinical practice-a case-based evaluation. J Med Econ. 2015b;18(2):96-105. doi:10.3111/13696998.2014.975234

Evans M, Chubb B, Gundgaard J. Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Adults with Type 1 and Type 2 Diabetes Mellitus. Diabetes Ther. 2017;8(2):275-291. doi:10.1007/s13300-017-0236-9

Evans M, Mehta R, Gundgaard J, Chubb B. Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting. Diabetes Ther. 2018;9(5):1919-1930. doi:10.1007/s13300-018-0478-1

Grima DT, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. Pharmacoeconomics. 2007;25(3):253-266. doi:10.2165/00019053-200725030-00007

Gschwend MH, Aagren M, Valentine WJ. Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. J Med Econ. 2009;12(2):114-123. doi:10.3111/13696990903080344

Haldrup S, Lapolla A, Gundgaard J, Wolden ML. Cost-effectiveness of switching to insulin degludec from other basal insulins in real-world clinical practice in Italy. J Med Econ. 2020;23(3):271-279.

Landstedt-Hallin L, Gundgaard J, Ericsson Å, Ellfors-Zetterlund S. Cost-effectiveness of switching to insulin degludec from other basal insulins: evidence from Swedish real-world data. Curr Med Res Opin. 2017;33(4):647-655.

Lalić N, Russel-Szymczyk M, Culic M, Tikkanen CK, Chubb B. Cost-Effectiveness of Insulin Degludec Versus Insulin Glargine U100 in Patients with Type 1 and Type 2 Diabetes Mellitus in Serbia. Diabetes Ther. 2018;9(3):1201-1216. doi:10.1007/s13300-018-0426-0

McEwan P, Poole CD, Tetlow T, Holmes P, Currie CJ. Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK. Curr Med Res Opin Suppl. 2007;23(1). doi:10.1185/030079906X167561

Palmer AJ, Weiss C, Sendi PP, et al. The cost-effectiveness of different management strategies for type I diabetes: a Swiss perspective. Diabetologia. 2000;43(1):13-26.

Mezquita-Raya P, Darbà J, Ascanio M, Ramírez de Arellano A. Cost-effectiveness analysis of insulin degludec compared with insulin glargine u100 for the management of type 1 and type 2 diabetes mellitus–from the Spanish National Health System perspective. Expert Rev Pharmacoeconomics Outcomes Res. 2017;17(6):587-595. doi:10.1080/14737167.2017.1345628

Morales C, de Luis D, de Arellano AR, Ferrario MG, Lizán L. Cost-Effectiveness Analysis of Insulin Detemir Compared to Neutral Protamine Hagedorn (NPH) in Patients with Type 1 and Type 2 Diabetes Mellitus in Spain. Diabetes Ther. 2015;6(4):593-610. doi:10.1007/s13300-015-0143-x

Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen KU. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Curr Med Res Opin. 2004;20(11):1729-1746.

Palmer AJ, Valentine WJ, Ray JA, et al. An economic assessment of analogue basal–bolus insulin versus human basal–bolus insulin in subjects with type 1 diabetes in the UK. Curr Med Res Opin. 2007;23(4):895-901.

Pedersen-Bjergaard U, Kristensen PL, Nørgaard K, et al. Short-term cost-effectiveness of insulin detemir and insulin aspart in people with type 1 diabetes who are prone to recurrent severe hypoglycemia. Curr Med Res Opin. 2016;32(10):1719-1725. doi:10.1080/03007995.2016.1205006

Pfohl M, Schädlich PK, Dippel FW, Koltermann KC. Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. J Med Econ. 2012;15(SUPPL. 2):14-27. doi:10.3111/13696998.2012.713879

Pollock RF, Tikkanen CK. A short-term cost-utility analysis of insulin degludec versus insulin glargine U100 in patients with type 1 or type 2 diabetes in Denmark. J Med Econ. 2017;20(3):213-220.

Pollock RF, Chubb B, Valentine WJ, Heller S. Evaluating the cost-effectiveness of insulin detemir versus neutral protamine hagedorn insulin in patients with type 1 or type 2 diabetes in the UK using a short-term modeling approach. Diabetes, Metab Syndr Obes Targets Ther. 2018;11:217-226. doi:10.2147/DMSO.S156739

Russel-Szymczyk M, Valov V, Savova A, Manova M. Cost-effectiveness of insulin degludec versus insulin glargine U100 in adults with type 1 and type 2 diabetes mellitus in Bulgaria. BMC Endocr Disord. 2019;19(1):1-10. doi:10.1186/s12902-019-0460-6

Tunis SL, Minshall ME, Conner C, et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: Modeling analysis. Curr Med Res Opin. 2009;25(5):1273-1284. doi:10.1185/03007990902869169

Valentine WJ, Palmer AJ, Erny-Albrecht KM, et al. Cost-effectiveness of basal insulin from a US health system perspective: Comparative analyses of detemir, glargine and NPH. Adv Ther. 2006;23(2):191-207. doi:10.1007/BF02850126

Valentine WJ, Aagren M, Haglund M, Ericsson Å, Gschwend MH. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in

patients with type 1 diabetes using a basal-bolus regimen in Sweden. Scand J Public Health. 2011;39(1):79-87.

Valentine WJ, Jendle J, Saraheimo M, Thorsteinsson B, Pollock RF, Lammert M. Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands. Diabet Med. 2012;29(3):303-312. doi:10.1111/j.1464-5491.2011.03461.x

1.1.14.3 Other references

Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin. 2004;20(sup1): S5-S26.

Appendices

Appendix A – Review protocols

Review protocol for long-acting insulins for optimal diabetic control

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Long-acting insulin therapies for optimal diabetic control
2.	Review question	In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus Neutral Protamine Hagedorn (NPH)) and frequency of administration for optimal diabetic control?
3.	Objective	To determine the clinical and cost effectiveness of different long-acting insulin therapies and frequency of administration for diabetic control in adults with Type 1 diabetes
4.	Searches	The following databases will be searched: Clinical searches: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR)

		• Embase • DARE • MEDLINE • MEDLINE In Process • MEDLINE ePubs • PsycINFO Economic searches: • Econlit • Embase • HTA • MEDLINE • MEDLINE In Process • MEDLINE ePubs • NHS EED • PsycINFO Searches will be restricted by: • English language

		• Study designs of RCTs and SRs • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results Other searches: • N/A The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Adults with Type 1 diabetes
6.	Population	Inclusion: Adults (aged 18 years and older) with type 1 diabetes Exclusion: • Adults with type 2 diabetes • Pregnant women with type 1, type 2 or gestational diabetes
7.	Intervention	Long acting insulins (once per day and twice per day regimens will be included):

		• Detemir (Levemir) • Degludec U100 (Tresiba) • Degludec U200 (Tresiba) • Glargine U100 (Lantus) • Glargine U300 (Toujeo) • NPH/ isophane/other intermediate (Humulin I, Insulatard, Insuman basal)) Biosimilar insulins, including but not limited to: • LY2963016 (Abasaglar) • MYL-1501D (Semglee) Long-acting insulins/biosimilar insulins will still be included if they are used in combination with short-acting or rapid acting insulins
B8.	Comparator	• Compared to each other • Same basal/long-acting insulin given either once/day or twice/day **Note:** comparison group should be on the same insulin regimen (e.g. rapid acting, short acting, intermediate, long acting or mixed insulin) as the treatment group

9.	Types of study to be included	• RCTs • Systematic reviews of RCTs
10.	Other exclusion criteria	• Studies with indirect, or mixed diabetes (type 1 diabetes and type 2 diabetes) populations will NOT be considered, unless data has been reported for the subgroup of type 1 diabetes patients, in which case this subgroup data will be used. • Studies comparing different doses of the same insulin • Non-English language studies • Conference abstracts
11.	Context	This review is part of an update of the NICE guideline on diabetes (type 1) in adults: diagnosis and management. This guideline covers adults (aged 18 years and older) with type 1 diabetes. This guideline will also cover all settings in which NHS care is received or commissioned.
12.	Primary outcomes (critical outcomes)	All outcomes will be grouped by duration of follow-up: short-term (≤6 months, or the one nearest to 6 months if multiple time-points are given) and long-term (>6 months, or the longest one if multiple time-points are given): • HbA1c (dichotomous or continuous, depending on how it is reported) • Hypoglycaemia (continuous, based on rates per patient, or dichotomous, separated into number of people experiencing an event, and number of events per person) including:

		○ Severe hypoglycaemia ○ Nocturnal hypoglycaemia • Diabetic ketoacidosis (dichotomous)
13.	Secondary outcomes (important outcomes)	All outcomes will be grouped by duration of follow-up: short-term (≤6 months, or the one nearest to 6 months if multiple time-points are given) and long-term (>6 months, or the longest one if multiple time-points are given): • Time in target glucose range • Time spent in hypoglycaemic range • Quality of life (continuous), including patient satisfaction - measured by validated tools (e.g. Short Form 12 (SF-12), Glucose Monitoring System Satisfaction Survey (GMSS), BG Monitoring System Rating Questionnaire (BGMSRQ), Hypoglycaemia Fear Survey- II (HFS-II), DQoL) • Adverse events, including ○ Cancer (dichotomous) ○ Injection site issues ○ Weight gain/loss (continuous) • Hospital admissions including: ○ Frequency of hospitalisations related to diabetes ○ Ambulance call-outs • Mental health outcomes measured using validated questionnaires (e.g. The Problem Areas in Diabetes (PAID) questionnaire and Diabetes Distress Scale (DSS): ○ Diabetes distress (including fear of hypoglycaemia, daily burden, treatment burden and diabetes burnout)

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Randomised control trials (individuals or cluster) will be assessed using the Cochrane risk of bias tool 2.0. Systematic reviews will be assessed using the ROBIS risk of bias tool
16.	Strategy for data synthesis	For details please see section 6 of Developing NICE guidelines: the manual

		Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3. In the pairwise analysis, subgroup analysis will also be conducted by frequency (e.g. once daily/ twice daily). Where sufficient data is available, a network meta-analysis will be conducted. Analysis will be performed in WinBugs14. Frequency will be explored in the NMA.

		Unit of analysis will be discrete triads of agent- concentration-frequency for example glargine U100 daily,g largine U100 twice daily and glargine U300 daily will all be separate nodes in the analysis and separate comparators in the HE analysis.
17.	Analysis of sub-groups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Co-interventions (such as different combinations of multiple daily injection therapy) • Baseline HbA1c (<7% vs >7%) • Elderly (aged 65 and above) and frail people • Baseline hypoglycaemia (mild, moderate or severe) • Diabetes duration (e.g. new onset diabetes or long standing type 1 diabetes) • People who require assistance for injections (including people requiring assistance due to physical disability reasons or mental-health related disability) • people with renal impairment • people of different ethnic backgrounds
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery

		☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐

		Risk of bias (quality) assessment	☐	☐	
		Data analysis	☐	☐	
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** Diabetesupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)			
25.	Review team members	From the Guideline Updates Team: • Dr Caroline Mulvihill • Ms Shreya Shukla • Dr Clare Dadswell • Mr Gabriel Rogers • Mr Thomas Jones • Ms Sarah Glover • Mr David Nicholls			
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.			

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10158
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Insulin therapy, long-term insulin therapy, type 1 diabetes, diabetic control, adults
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]

36.	Details of final publication	www.nice.org.uk

Appendix B – Methods

This guideline was developed using the methods described in the 2018 NICE guidelines manual.

Declarations of interest were recorded according to the NICE conflicts of interest policy.

Developing the review questions and outcomes

The review question was developed for this guideline was based on the key areas identified in the guideline framework document. They were drafted by the NICE guideline updates team and refined and validated by the guideline committee.

The review questions were based on the following frameworks:

- Population, Intervention, Comparator and Outcome [and Study type] (PICO[S]) for reviews of interventions

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Reviewing research evidence

Evidence was searched for each review question using the methods specified in the 2018 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The evidence review made use of the priority screening functionality within the EPPI-reviewer software. This functionality uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being ‘includes’ or ‘excludes’ during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened. In this review, all records were screened.

As an additional check to ensure this approach did not miss relevant studies, systematic reviews were included in the review protocol and search strategy for all review questions. Relevant systematic reviews or qualitative evidence syntheses were used to identify any papers not found through the primary search. Committee members were also consulted to identify studies that were missed. If additional studies were found that were erroneously excluded during the priority screening process, the full database was subsequently screened.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence review and relevant data was included).

Methods of combining evidence

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. Network meta-analyses was considered in situations where the following criteria were met:

- At least three treatment alternatives.
- The aim of the review was to produce recommendations on the most effective option, rather than simply describe the effectiveness of treatment alternatives.

In other situations, pairwise meta-analysis was used to compare interventions.

Pairwise meta-analysis

Pairwise meta-analyses were performed in Cochrane Review Manager V5.3. A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).A pooled mean difference was calculated for continuous outcomes (using the inverse variance method) when the same scale was used to measure an outcome across different studies.

For continuous outcomes analysed as mean differences, change from baseline values were used in the meta-analysis if they were accompanied by a measure of spread (for example standard deviation). If studies only reported baseline and final time point values, change from baseline was calculated. Change from baseline standard deviations were estimated, assuming a correlation coefficient derived from studies reporting both baseline and endpoint data, or if no such studies were available, assuming a correlation of 0.5 as a conservative estimate (Follman et al., 1992; Fu et al., 2013). If only a subset of trials reported change from baseline data, final timepoint values were combined with change from baseline values to produce summary estimates of effect.

Random effects models were fitted when there was significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.

For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with $I^2 < 50\%$) the results from these subgroups were reported using fixed effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

During data extraction, it was identified that a number of trials included a titration phase and maintenance. Reporting of outcomes, particularly hypoglycaemic events varied across these

studies. For example, a number of studies were identified (for example, Pieber 2005, Vague 2003, Standl 2004 and Russell-Jones 2004) which included a titration phase and maintenance phase, but only reported data from the maintenance phase. However, one study was identified (Pieber 2007) which reported data separately for the two phases. To ensure consistency in data extraction, data from the maintenance phase was extracted, if available. Additionally, it was also noted that data from the maintenance phase would be more representative of what is seen is seen clinically.

Network meta-analysis

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of the TSDs was used without substantive alteration to specify synthesis models where appropriate. For event rate, a shared parameter model was used (Keeney 2018) based on the TSD codes, as described below.

In all models, results were assessed for convergence to determine the length of 'burn in' period required by examining the 'bgdiag' and 'history' plots. Additionally, the MC error was assessed to check that it was sufficiently small (less than 5% of the standard deviation of the posterior distribution for each parameter) and additional samples were summarised if this was not the case.

Change in HbA1c NMA

Three separate chains with different initial values were used. Results were reported summarising 100,000 samples from the posterior distribution of each model, having run and discarded the 'burn-in' iterations.

All hypoglycaemia and severe/major hypoglycaemia NMA

Some studies reported data on event rates, some reported data on the risk of event, and some reported both. A shared parameter approach (as outlined by Keeney et al., 2018) was used to combine all studies reporting rates or risk by modelling treatment effects on event rates. This was done for all hypoglycaemia and also for severe hypoglycaemia. In this approach, the following models from TSD2 were used:

- Binomial likelihood with a clog-log function for risk data
- Poisson likelihood with a log-link function for rate data.

Rate data was preferred because it more directly provides information on event rates. Therefore where possible, rate data was extracted or was estimated using the information provided in the studies and person-years was calculated. For studies which did not report rate data, risk data was extracted and included in the model using the binomial likelihood.

Two separate chains with different initial values were used. Results were reported summarising 70,000 samples from the posterior distribution of each model, having run and discarded the 'burn-in' iterations.

Nocturnal hypoglycaemia

A conditional probabilities approach was used to model nocturnal hypoglycaemia. This model used a binomial logit function, where the numerator was the number of nocturnal events and the denominator was the number of all hypoglycaemic events.

Three separate chains with different initial values were used. Results were reported summarising 70,000 samples from the posterior distribution of each model, having run and discarded the 'burn-in' iterations.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned Normal (0, 10000) priors, and the between-trial standard deviations used in random-effects models for dichotomous outcomes were given Uniform (0, 5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

Fixed - and random-effects models were explored for each outcome, with the final choice of model based on the total residual deviance and deviance information criterion (DIC): if DIC was at least 3 points lower for the random-effects model, it was preferred; otherwise, the fixed effects model was considered to provide an equivalent fit to the data in a more parsimonious analysis and was preferred.

Inconsistency between direct and indirect evidence was assessed when possible by fitting 'inconsistency models' to the data and assessing model fit using the deviance information criteria, residual deviance and between studies standard deviation. A reduction in DIC of 3 or more was taken as evidence of inconsistency. If inconsistency was identified, the source of this inconsistency was explored and resolved if possible (for example by re-evaluating which studies are included in the network). If inconsistency could not be resolved then this was reflected in the quality assessment for the network meta-analysis (see Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. This evidence is presented in Appendix H. This evidence has been summarised narratively in section 1.1.11.

Modified GRADE for intervention studies analysed using network meta-analysis)

Appraising the quality of evidence

Intervention studies (relative effect estimates)

Parallel RCTs and cross-over RCTs were quality assessed using the Cochrane Risk of Bias Tool 2.0. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

One of the main concerns with cross-over studies is the possibility of a 'carry over' effect. This means that the treatment effect from one period is carried over to the next period which can introduce bias. Due to this risk of bias, data from first period of the crossover trial was utilised, if available. If this information was not available or the trial presented combined results from both periods, the best available data was utilised and the study was appropriately downgraded.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. Clinical decision threshold that were used in the guideline are given in **Error! Reference source not found.** and also reported in the relevant evidence reviews.

Table 1: Identified Clinical decision thresholds

Outcome	Clinical decision threshold	Source
HbA1c (presented as a percentage or mmol/l)	0.5 percentage points (5.5 mmol/ mol)	Little 2013
Time in range (%)	5% change in time in range	Batelino 2019

For continuous outcomes expressed as a mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For relative risks and hazard ratios, where no other clinical decision threshold was available, line of no effect was used.

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from parallel and crossover randomised controlled trials were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in **Error! Reference source not found.**.

Table 2: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. This evidence is presented in Appendix H. This evidence has been summarised narratively in section 1.1.11.

Modified GRADE for intervention studies analysed using network meta-analysis

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the

network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA to judge the overall strength of evidence. Additionally, where appropriate, threshold analysis was considered to explore the uncertainties within the NMA at contrast level.

Table 3: Rationale for downgrading quality of evidence for network meta-analysis

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses conducted under a Bayesian framework, the network was downgraded one level if the DIC for an inconsistency model was more than 3 points lower than the corresponding consistency model.
Imprecision	95% Credible intervals were used to assess imprecision. Not serious: The data were sufficiently precise to allow the committee to draw conclusions from the results of the NMA. Serious: Imprecision had a moderate impact on the ability of the committee to draw conclusions from the results of the NMA. Very serious: Imprecision had a substantial impact on the committee to draw conclusions from the results of the NMA.

Follmann D, Elliott P, Suh I, Cutler J (1992) Variance imputation for overviews of clinical trials with continuous response. Journal of Clinical Epidemiology 45:769–73

Fu R, Vandermeer BW, Shamliyan TA, et al. (2013) Handling Continuous Outcomes in Quantitative Synthesis In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK154408/

Keeney E, Dawoud D, Dias S (2018) Different Methods for Modelling Severe Hypoglycaemic Events: Implications for Effectiveness, Costs and Health Utilities. PharmacoEconomics (2018) 36:523–532

Batelino T, Danne T, Bergenstal RM et al. (2019) Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From The International Consensus On Time In Range. Diabetes care 42(8): 1593-1603

Little RR and Rohlfing CL (2013) The Long And Wining Road To Optimal Hba1c Measurement. Clinica chimca acta; international journal for clinical chemistry 418: 63-71

Appendix C – Literature search strategies

Clinical evidence

Database: Medline
1 exp Diabetes Mellitus, Type 1/ (75446)
2 Diabetic Ketoacidosis/ (6369)
3 ((diabet* or DM) adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1)).tw. (48994)
4 (diabet* adj4 (autoimmun* or auto immun*)).tw. (6103)
5 lada.tw. (527)
6 (diabet* adj4 (brittle or labile)).tw. (444)
7 (diabet* adj4 (sudden onset or majority onset or juvenile or childhood or adolescen*)).tw. (8726)
8 (diabet* adj4 (keto* or acido* or gastropare*)).tw. (7302)
9 (dm1 or iddm or t1d* or dka).tw. (18936)
10 ((diabet* adj4 (insulin depend* or insulin deficien*)) not non insulin depend*).tw. (16133)
11 diabetes mellitus.ti. (62972)
12 ((diabet* or DM) adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti. (57069)
13 11 not 12 (47824)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 13 (134889)
15 exp Insulin, Long-Acting/ (3965)

16 Biphasic insulins/ (225)

17 ((long-act* or longact* or "long act*" or ultralong* or ultra-long* or "ultra long*" or semilent* or ultralent* or lent* or biphas* or mix* or basal*) adj4 insulin*).tw. (10732)

18 (Detemir or Levemir).tw. (724)

19 (Degludec or Tresiba or Xultrophy or Xultophy).tw. (362)

20 (Glargine or Lantus or Solostar or Suliqua or Soliqua).tw. (2159)

21 (Isophane or NPH or Protamine or Protophan* or Insulatard or Humulin or Insuman or infusat or Novomix or Novolin or Actrapid or Hypurin or Novolin or Exubera or Myxredlin or Afrezza).tw. (9647)

22 monotard.tw. (69)

23 Biosimilar Pharmaceuticals/ (1971)

24 (biosimilar* or bio-similar* or BioIns*).tw. (4956)

25 ((follow* or subsequent* or similar*) adj2 biologic*).tw. (5338)

26 (Abasaglar or Basaglar or Basalog or Basalin or Toujeo or Admelog or Lusduna or Lusdana or Semglee or Glaritus or Glarzia).tw. (33)

27 (SAR342434 or MYL-1501D or MK-1293 or LY2963016).tw. (28)

28 or/15-27 (31782)

29 14 and 28 (3229)

30 randomized controlled trial.pt. (505848)

31 randomi?ed.mp. (789572)

32 placebo.mp. (193553)

33 or/30-32 (840997)

34 (MEDLINE or pubmed).tw. (160400)

35 systematic review.tw. (118166)

36 systematic review.pt. (127054)

37 meta-analysis.pt. (114906)

38 intervention$.ti. (122165)

39 or/34-38 (373618)

40 33 or 39 (1107863)

41 29 and 40 (803)

42 animals/ not humans/ (4667663)

43 41 not 42 (795)

44 limit 43 to english language (766)

Database: MIP

1 exp Diabetes Mellitus, Type 1/ (0)

2 Diabetic Ketoacidosis/ (0)

3 ((diabet* or DM) adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1)).tw. (6282)

4 (diabet* adj4 (autoimmun* or auto immun*)).tw. (608)

5 lada.tw. (83)

6 (diabet* adj4 (brittle or labile)).tw. (26)

7 (diabet* adj4 (sudden onset or majority onset or juvenile or childhood or adolescen*)).tw. (756)

8 (diabet* adj4 (keto* or acido* or gastropare*)).tw. (1040)

9 (dm1 or iddm or t1d* or dka).tw. (2733)

10 ((diabet* adj4 (insulin depend* or insulin deficien*)) not non insulin depend*).tw. (444)

11 diabetes mellitus.ti. (7828)

12 ((diabet* or DM) adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti. (11491)

13 11 not 12 (4234)

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 13 (11431)

15 exp Insulin, Long-Acting/ (0)

16 Biphasic insulins/ (0)

17 ((long-act* or longact* or "long act*" or ultralong* or ultra-long* or "ultra long*" or semilent* or ultralent* or lent* or biphas* or mix* or basal*) adj4 insulin*).tw. (1048)

18 (Detemir or Levemir).tw. (161)

19 (Degludec or Tresiba or Xultrophy or Xultophy).tw. (175)

20 (Glargine or Lantus or Solostar or Suliqua or Soliqua).tw. (448)

21 (Isophane or NPH or Protamine or Protophan* or Insulatard or Humulin or Insuman or infusat or Novomix or Novolin or Actrapid or Hypurin or Novolin or Exubera or Myxredlin or Afrezza).tw. (868)

22 monotard.tw. (0)

23 Biosimilar Pharmaceuticals/ (0)

24 (biosimilar* or bio-similar* or BioIns*).tw. (2103)

25 ((follow* or subsequent* or similar*) adj2 biologic*).tw. (627)

26 (Abasaglar or Basaglar or Basalog or Basalin or Toujeo or Admelog or Lusduna or Lusdana or Semglee or Glaritus or Glarzia).tw. (11)

27 (SAR342434 or MYL-1501D or MK-1293 or LY2963016).tw. (8)

28 or/15-27 (4766)

29 14 and 28 (345)

30 randomized controlled trial.pt. (277)

31 randomi?ed.mp. (73826)

32 placebo.mp. (18195)

33 or/30-32 (80241)

34 (MEDLINE or pubmed).tw. (34924)

35 systematic review.tw. (28743)

36 systematic review.pt. (880)

37 meta-analysis.pt. (48)

38 intervention$.ti. (21006)

39 or/34-38 (67099)

40 33 or 39 (132316)

41 29 and 40 (84)

42 animals/ not humans/ (1)

43 41 not 42 (84)

44 limit 43 to english language (82)

Database: EMBASE

1 exp insulin dependent diabetes mellitus/ (113938)

2 diabetic ketoacidosis/ (11994)

3 ((diabet* or DM) adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1)).tw. (87488)

4 (diabet* adj4 (autoimmun* or auto immun*)).tw. (9366)

5 lada.tw. (982)

6 (diabet* adj4 (brittle or labile)).tw. (679)

7 (diabet* adj4 (sudden onset or majority onset or juvenile or childhood or adolescen*)).tw. (13282)

8 (diabet* adj4 (keto* or acido* or gastropare*)).tw. (12398)

9 (dm1 or iddm or t1d* or dka).tw. (38881)

10 ((diabet* adj4 (insulin depend* or insulin deficien*)) not non insulin depend*).tw. (19688)

11 diabetes mellitus.ti. (90339)

12 ((diabet* or DM) adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti. (105614)

13 11 not 12 (61507)

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 13 (204002)

15 exp long acting insulin/ (1879)

16 biphasic insulin/ (737)

17 ((long-act* or longact* or "long act*" or ultralong* or ultra-long* or "ultra long*" or semilent* or ultralent* or lent* or biphas* or mix* or basal*) adj4 insulin*).tw. (18851)

18 (Detemir or Levemir).tw. (2403)

19 (Degludec or Tresiba or Xultrophy or Xultophy).tw. (1449)

20 (Glargine or Lantus or Solostar or Suliqua or Soliqua).tw. (6781)

21 (Isophane or NPH or Protamine or Protophan* or Insulatard or Humulin or Insuman or infusat or Novomix or Novolin or Actrapid or Hypurin or Novolin or Exubera or Myxredlin or Afrezza).tw. (19243)

22 monotard.tw. (666)

23 biosimilar agent/ (4494)

24 (biosimilar* or bio-similar* or BioIns*).tw. (10826)

25 ((follow* or subsequent* or similar*) adj2 biologic*).tw. (8149)

26 (Abasaglar or Basaglar or Basalog or Basalin or Toujeo or Admelog or Lusduna or Lusdana or Semglee or Glaritus or Glarzia).tw. (236)

27 (SAR342434 or MYL-1501D or MK-1293 or LY2963016).tw. (100)

28 or/15-27 (59690)

29 14 and 28 (8480)

30 random:.tw. (1532966)

31 placebo:.mp. (452764)

32 double-blind:.tw. (208926)

33 or/30-32 (1786809)

34 (MEDLINE or pubmed).tw. (254610)

35 exp systematic review/ or systematic review.tw. (293864)

36 meta-analysis/ (186798)
37 intervention$.ti. (197011)
38 or/34-37 (646388)
39 33 or 38 (2230191)
40 29 and 39 (1948)
41 limit 40 to english language (1884)
42 nonhuman/ not human/ (4616295)
43 41 not 42 (1858)
44 (conference abstract or conference paper or conference proceeding or "conference review").pt. (4554974)
45 43 not 44 (1191)
Database: PscyhINFO
1 exp Diabetes Mellitus/ (8342)
2 ((diabet* or DM) adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1)).tw. (2762)
3 (diabet* adj4 (autoimmun* or auto immun*)).tw. (77)
4 lada.tw. (11)
5 (diabet* adj4 (brittle or labile)).tw. (25)
6 (diabet* adj4 (sudden onset or majority onset or juvenile or childhood or adolescen*)).tw. (1347)
7 (diabet* adj4 (keto* or acido* or gastropare*)).tw. (191)
8 (dm1 or iddm or t1d* or dka).tw. (1050)
9 ((diabet* adj4 (insulin depend* or insulin deficien*)) not non insulin depend*).tw. (827)
10 diabetes mellitus.ti. (2232)
11 ((diabet* or DM) adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti. (3384)
12 10 not 11 (1541)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 12 (11143)
14 exp Insulin/ (3715)
15 ((long-act* or longact* or "long act*" or ultralong* or ultra-long* or "ultra long*" or semilent* or ultralent* or lent* or biphas* or mix* or basal*) adj4 insulin*).tw. (135)
16 (Detemir or Levemir).tw. (10)

17 (Degludec or Tresiba or Xultrophy or Xultophy).tw. (2)
18 (Glargine or Lantus or Solostar or Suliqua or Soliqua).tw. (24)
19 (Isophane or NPH or Protamine or Protophan* or Insulatard or Humulin or Insuman or infusat or Novomix or Novolin or Actrapid or Hypurin or Novolin or Exubera or Myxredlin or Afrezza).tw. (248)
20 monotard.tw. (0)
21 Biosimilar Pharmaceuticals/ (0)
22 (biosimilar* or bio-similar* or BioIns*).tw. (67)
23 ((follow* or subsequent* or similar*) adj2 biologic*).tw. (370)
24 (Abasaglar or Basaglar or Basalog or Basalin or Toujeo or Admelog or Lusduna or Lusdana or Semglee or Glaritus or Glarzia).tw. (0)
25 (SAR342434 or MYL-1501D or MK-1293 or LY2963016).tw. (0)
26 or/14-25 (4411)
27 13 and 26 (898)
28 randomized controlled trial.pt. (0)
29 randomi?ed.mp. (83541)
30 placebo.mp. (40212)
31 or/28-30 (108425)
32 (MEDLINE or pubmed).tw. (22666)
33 systematic review.tw. (27588)
34 systematic review.pt. (0)
35 meta-analysis.pt. (0)
36 intervention$.ti. (70440)
37 or/32-36 (106806)
38 31 or 37 (197606)
39 27 and 38 (91)
40 animals/ not humans/ (7235)
41 39 not 40 (91)
42 limit 41 to english language (88)
Database: Cochrane

#1 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees 5394

#2 MeSH descriptor: [Diabetic Ketoacidosis] this term only 129

#3 ((diabet* or DM) near/4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1)):ti,ab,kw 9838

#4 (diabet* near/4 (autoimmun* or auto immun*)):ti,ab,kw 891

#5 lada:ti,ab,kw 65

#6 (diabet* near/4 (brittle or labile)):ti,ab,kw 15

#7 (diabet* near/4 (sudden onset or majority onset or juvenile or childhood or adolescen*)):ti,ab,kw 2617

#8 (diabet* near/4 (keto* or acido* or gastropare*)):ti,ab,kw 897

#9 (dm1 or iddm or t1d* or dka):ti,ab,kw 3148

#10 ((diabet* near/4 (insulin depend* or insulin deficien*)) not non insulin depend*):ti,ab,kw 3632

#11 diabetes mellitus:ti 9790

#12 ((diabet* or DM) near/4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)):ti 22698

#13 #11 NOT #12 3961

#14 {OR #1-#10, #13} 15905

#15 MeSH descriptor: [Insulin, Long-Acting] explode all trees 1885

#16 MeSH descriptor: [Biphasic Insulins] this term only 192

#17 ((long-act* or longact* or long act* or ultralong* or ultra-long* or ultra long* or semilent* or ultralent* or lent* or biphas* or mix* or basal*) near/4 insulin*):ti,ab,kw 7116

#18 (Detemir or Levemir):ti,ab,kw 683

#19 (Degludec or Tresiba or Xultrophy or Xultophy):ti,ab,kw 892

#20 (Glargine or Lantus or Solostar or Suliqua or Soliqua):ti,ab,kw 2663

#21 (Isophane or NPH or Protamine or Protophan* or Insulatard or Humulin or Insuman or infusat or Novomix or Novolin or Actrapid or Hypurin or Novolin or Exubera or Myxredlin or Afrezza):ti,ab,kw 2207

#22 (monotard):ti,ab,kw 22

#23 MeSH descriptor: [Biosimilar Pharmaceuticals] this term only 148

#24 (biosimilar* or bio-similar* or BioIns*):ti,ab,kw 1013

#25 ((follow* or subsequent* or similar*) near/2 biologic*):ti,ab,kw 216

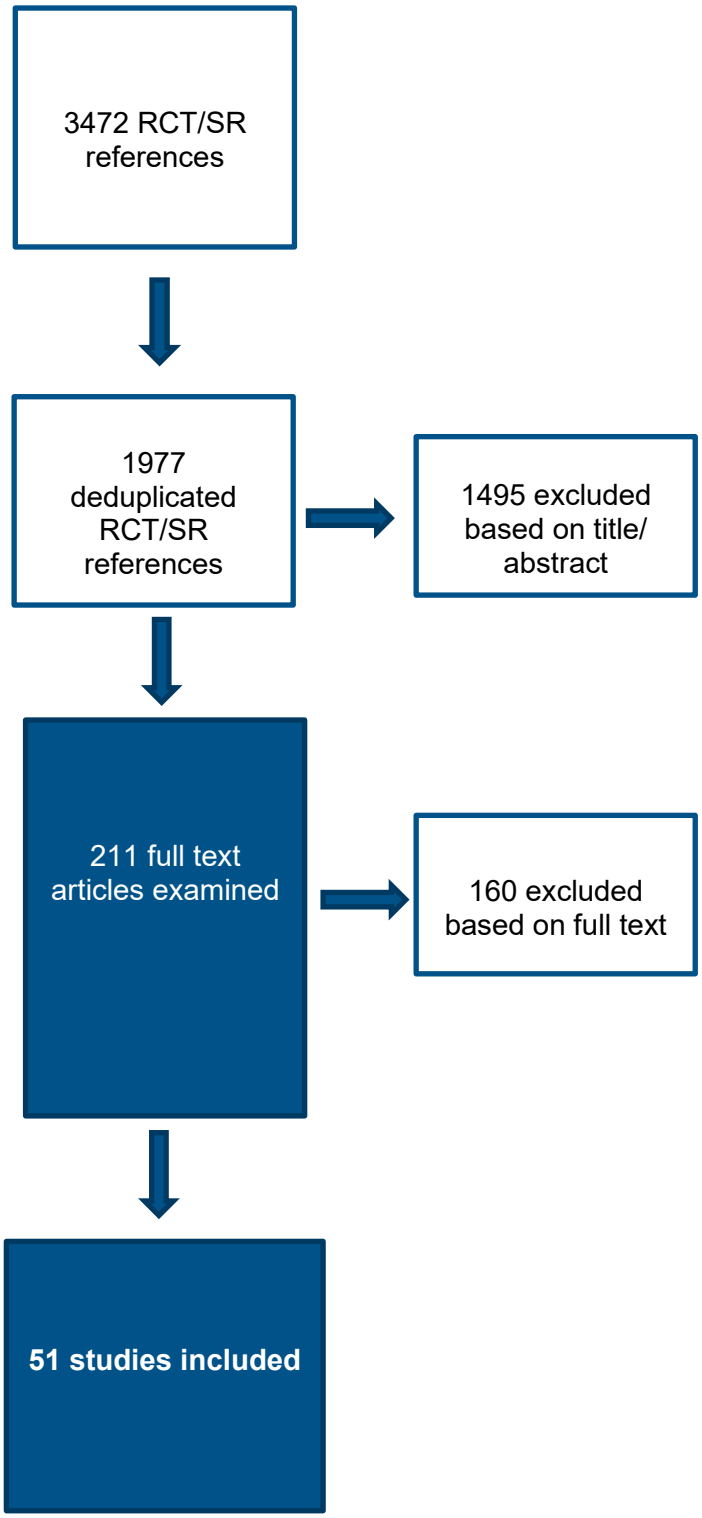
#26 (Abasaglar or Basaglar or Basalog or Basalin or Toujeo or Admelog or Lusduna or Lusdana or Semglee or Glaritus or Glarzia):ti,ab,kw 47 #27 (SAR342434 or MYL-1501D or MK-1293 or LY2963016):ti,ab,kw 99 #28 {OR #15-#27} 10528 #29 #14 AND #28 2528 #30 "conference":pt or (clinicaltrials or trialsearch):so 485953 #31 #29 NOT #30 1298 #32 "www.who.int":so 134011 #33 #31 NOT #32 1298

Database: CRD (DARE)

1	MeSH DESCRIPTOR Diabetes Mellitus, Type 1 EXPLODE ALL TREES IN DARE	146
2	MeSH DESCRIPTOR Diabetic Ketoacidosis IN DARE	5
3	(((diabet* or DM) near4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1))) IN DARE	178
4	((diabet* near4 (autoimmun* or auto immun*))) IN DARE	0
5	(lada) IN DARE	1
6	((diabet* near4 (brittle or labile))) IN DARE	0
7	((diabet* near4 (sudden onset or majority onset or juvenile or childhood or adolescen*))) IN DARE	12
8	((diabet* near4 (keto* or acido* or gastropare*))) IN DARE	19
9	((dm1 or iddm or t1d* or dka)) IN DARE	7
10	(((diabet* near4 (insulin depend* or insulin deficien*)) not non insulin depend*)) IN DARE	0
11	(diabetes mellitus):TI IN DARE	373

12	((((diabet* or DM) near4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))):TI IN DARE	4
13	#11 NOT #12	371
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13	527
15	MeSH DESCRIPTOR Insulin, Long-Acting EXPLODE ALL TREES IN DARE	31
16	MeSH DESCRIPTOR Biphasic Insulins IN DARE	4
17	(((long-act* or longact* or long act* or ultralong* or ultra-long* or ultra long* or semilent* or ultralent* or lent* or biphas* or mix* or basal*) near4 insulin*)) IN DARE	52
18	((Detemir or Levemir)) IN DARE	21
19	((Degludec or Tresiba or Xultrophy or Xultophy)) IN DARE	2
20	((Glargine or Lantus or Solostar or Suliqua or Soliqua)) IN DARE	42
21	((Isophane or NPH or Protamine or Protophan* or Insulatard or Humulin or Insuman or infusat or Novomix or Novolin or Actrapid or Hypurin or Novolin or Exubera or Myxredlin or Afrezza)) IN DARE	43
22	((monotard)) IN DARE	0
23	MeSH DESCRIPTOR Biosimilar Pharmaceuticals IN DARE	2
24	((biosimilar* or bio-similar* or BioIns*)) IN DARE	5
25	(((follow* or subsequent* or similar*) near2 biologic*)) IN DARE	8
26	((Abasaglar or Basaglar or Basalog or Basalin or Toujeo or Admelog or Lusduna or Lusdana or Semglee or Glaritus or Glarzia)) IN DARE	0
27	((SAR342434 or MYL-1501D or MK-1293 or LY2963016)) IN DARE	0
28	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	93
29	#14 AND #28	40

Appendix D – Effectiveness evidence study selection



Appendix E – Effectiveness evidence

Ashwell 2006

Ashwell, 2006

Bibliographic Reference	Ashwell, S G; Gebbie, J; Home, P D; Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart.; Diabetic medicine : a journal of the British Diabetic Association; 2006; vol. 23 (no. 8); 879-86

Study details

Study type	Crossover randomised controlled trial
Trial registration number	Not provided
Study location	UK
Study setting	Not specified
Study dates	Not provided. Study was accepted for publication in 2006.
Duration of follow-up	4 weeks
Sources of funding	Sanofi-Aventis
Sample size	20
Inclusion criteria	Aged 18 years and above Aged 18-65 years History of Type 1 diabetes Already taking insulin Had been using a multiple insulin injection regimen for at least 1 year. C-peptide concentration Random concentration of ≤ 0.18 nmol/l
Exclusion criteria	Proliferative retinopathy or maculopathy Recurrent major hypoglycaemia Impaired hepatic or renal function Night shift workers Women of childbearing potential not using adequate contraception
Method of allocation	After a 1-week screening period during which previous insulin therapy was continued, participants were randomised by a third party (concealed randomization). [No further details are provided]
Intervention(s)	Insulin glargine injected once daily at dinner-time with insulin aspart taken at main meals.
Comparator	Insulin glargine injected twice daily at breakfast- and dinner-times with insulin aspart taken at main meals. People randomised to twice-daily insulin glargine initially received 50% of the total daily basal insulin dose at breakfast time and 50% at dinner-time.

Outcome measures	**HbA1c** HbA1c (%) at follow up - data used to calculate change in HbA1c (%) **Hypoglycaemia** • Hypoglycaemia (all) • Severe hypoglycaemia Hypoglycaemia was classified as anytime symptomatic (appropriate symptoms confirmed by SMBG < 3.5 mmol/l and selftreated), anytime severe (requiring third party assistance), and any nocturnal (from bedtime until measurement of pre-breakfast blood glucose concentration). • Nocturnal hypoglycaemia
Loss to follow up	None

Study arms

Glargine once daily (N = 20) Glargine U100 given once daily at dinner time with insulin aspart taken at main meals (period 1). Glargine U100 given twice daily at breakfast- and dinner times with insulin aspart taken at main meals (period 2).
Glargine twice daily (N = 20) Glargine U100 given twice daily at breakfast- and dinner times with insulin aspart taken at main meals (period 1). Glargine U100 given once daily at dinner time with insulin aspart taken at main meals (period 2).

Characteristics

Study-level characteristics

	Study (N = 20)
% Female	
Sample Size	n = 8 ; % = 40
Mean age (SD)	
Mean/SD	43.4 (13.7)
BMI	
Mean/SD	26.7 (4.5)

Cochrane risk of bias tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No washout period.)
	Overall Directness	Directly applicable

Bartley 2008

Bartley, 2008

Bibliographic Reference	Bartley, P C; Bogoev, M; Larsen, J; Philotheou, A; Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial.; Diabetic medicine : a journal of the British Diabetic Association; 2008; vol. 25 (no. 4); 442-9

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	10 countries (not reported)
Study setting	33 investigational sites
Study dates	Not reported
Duration of follow-up	24 months
Sources of funding	Novo-Nordisk, Sanofi-Aventis and Neurocrine Biosciences Inc.
Sample size	497
Inclusion criteria	Aged 18 years and above HbA1c ≤11.0% BMI ≤35.0 kg/m² History of Type 1 diabetes ≥1 year Treated on a basal-bolus insulin regimen. For ≥3 months Able to self-measure plasma glucose
Exclusion criteria	Proliferative retinopathy or maculopathy Other significant medical disorders Recurrent major hypoglycaemia Allergy to insulin Pregnant or breast-feeding women
Method of allocation	Patients were randomised to detemir or NPH in a 2:1 ratio using a telephone randomisation system. Because detemir and NPH are visually distinguishable and patients were to self-administer insulin throughout the trial, an open- labelled design was used.
Intervention(s)	Once or twice daily Once-daily Detemir (Levemir 100 U/ml) with insulin Aspart (NovoRapid 100 U/ml). Basal insulin administered at any time during the evening. Bolus insulin injected immediately before each main meal. Basal insulin titrated individually throughout the trial aiming for a PG target ≤ 6.0 mmol/l before breakfast and dinner. Bolus insulin was titrated according to local practice to achieve a post-prandial PG level ≤9.0 mmol/l. A second basal insulin dose could be added in the morning if the pre-dinner PG target was not achieved with use of the algorithm and after optimization of bolus insulin.

Comparator	Once or twice daily Once-daily basal insulin dose of NPH (Insulatard 100 IU/ml) with insulin Aspart (NovoRapid 100 U/ml). Timing of insulin doses and PG targets were the same as those used for the intervention arm. A second basal insulin dose could be added in the morning if the pre-dinner PG target was not achieved with use of the algorithm and after optimization of bolus insulin.
Outcome measures	**HbA1c** • HbA1c at follow up -Change in HbA1c could not be calculated as baseline data was presented as mean and range. • Patients achieved an HbA1c ≤7.0 % • Patients achieved an HbA1c ≤7.0 % in the absence of confirmed hypoglycaemia. **Hypoglycaemia** • Hypoglycaemia (all)- Classified as major if assistance from another person was required, as minor if PG < 3.1 mmol/l and the individual dealt with the episode him/herself, and as symptoms only if episodes were not confirmed by a PG measurement and no assistance was required. • Major hypoglycaemia - number of patients having at least one hypoglycaemic episode. • Nocturnal hypoglycaemia Defined as hypoglycaemic episodes occurring between 23:00-06:00. **Adverse events** • Adverse events - possibly or probably related to trial drug • Serious adverse events - possibly or probably related to trial drug **Body weight** • Weight at follow up (24 months) Change in weight could not be calculated as baseline data was presented as mean and range.
Loss to follow up	52 discontinued treatment in the detemir arm: adverse events (13), ineffective treatment (2), non-compliance (6), other reasons (31) 22 discontinued treatment in the NPH arm: adverse events (1), ineffective treatment (2), non-compliance (6), other reasons (13)
Additional comments	A total of 37% of patients completed the trial on a once-daily detemir regimen compared to 45% on NPH. The median time to transfer from a once-daily to a twice-daily regimen was approximately 9 months with both treatments (NS).

Study arms

Detemir (N = 331) Once-daily or twice basal insulin dose of Detemir (Levemir 100 U/ml) with bolus dose of insulin Aspart (NovoRapid 100 U/ml)
NPH (N = 166)

Detemir (N = 331)
Once-daily or twice basal insulin dose of Detemir (Levemir 100 U/ml) with bolus dose of insulin Aspart (NovoRapid 100 U/ml)
Once-daily or twice basal insulin dose of NPH (Insulatard 100 IU/ml) with bolus dose of insulin Aspart (NovoRapid 100 U/ml)

Characteristics

Arm-level characteristics

	Detemir (N = 331)	NPH (N = 166)
% Female (%)		
Nominal	44.4	47
Age (mean, range) (years)		
Custom value	35 (18-75)	35 (18-70)
BMI (mean, range) (kg/m²)		
Custom value	24.7 (15.4-34.6)	24.7 (16.9-34.7)
HbA1c (mean, range) (%)		
Custom value	8.3 (5.0-11.6)	8.4 (5.3-11.4)
Basal insulin dose (mean, range) (IU/kg)		
Custom value	0.37 (0.04–1.10)	0.36 (0.06–1.24)
Meal-time insulin dose (mean, range) (IU/kg)		
Custom value	0.46 (0.02–1.67)	0.45 (0.03–1.29)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Open label trial - blinding not possible because of detemir and NPH are visually distinguishable. Potential bias in subjective outcomes e.g. adverse events.)

Cochrane Risk of Bias Tool 2.0		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (More patients withdrew from detemir arm because of AE.)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (More patients withdrew from the detemir arm than the NPH arm due to adverse events. Open lable trial could have influenced subjective outcomes such as adverse events.)
	Overall Directness	Directly applicable

Bergenstal 2017

Bergenstal, 2017

Bibliographic Reference	Bergenstal, Richard M; Bailey, Timothy S; Rodbard, David; Ziemen, Monika; Guo, Hailing; Muehlen-Bartmer, Isabel; Ahmann, Andrew J; Comparison of Insulin Glargine 300 Units/mL and 100 Units/mL in Adults With Type 1 Diabetes: Continuous Glucose Monitoring Profiles and Variability Using Morning or Evening Injections.; Diabetes care; 2017; vol. 40 (no. 4); 554-560

Study details

Study type	Crossover randomised controlled trial
Trial registration number	NCT01658579
Study location	USA
Study setting	3 centres
Study dates	August 2012- May 2013
Duration of follow-up	16 weeks (Two 8 week crossover periods)
Sources of funding	Sanofi sponsored this study and was responsible for designing and coordinating the trial. Sanofi monitored the clinical sites, collected and managed the data, and performed all statistical analyses.
Sample size	59
Inclusion criteria	Adult participants (≥18 and <70 years of age at screening) diagnosed with type 1 diabetes and receiving any basal insulin regimen and mealtime insulin analog for at least 1 year were eligible for inclusion.
Exclusion criteria	HbA1c >9.0% at screening; not taking a stable insulin dose in the 30 days before screening; use of an insulin pump within 6 months before screening; use of premixed insulin, human regular insulin as mealtime insulin, and/or any antihyperglycemic drugs other than an insulin analog at mealtime and basal insulin within 3 months before screening; and any contraindication to insulin glargine.
Method of allocation	After a 4 week screening phase, participants were randomised 1:1:1:1, using a remote telephone system to receive treatment with glargine U300 or U100 in the morning or evening during treatment period A (week1-8), participants then crossed over to the alternate injection schedule (evening or morning) for treatment period B (9-16)
Intervention(s)	Glargine U300 Participants self-administered subcutaneous injections of Gla-300 at the same time each day, either morning (immediately before breakfast until lunch) or evening (immediately before the evening mela until bedtime). Injections were administered using commercially available insulin syringes because an insulin pen that could deliver the small volumes of Gla-300 required was not available when the study was conducted. The basal insulin dose was titrated no more often than every 3 to 4 days during the first 6 weeks of each treatment period (A and B) to reach the target fasting SMPG of 80–130mg/dL (4.4–7.2mmol/L), and it was optimized by the investigators using CGM data (downloaded at the study visits). Each participant continued to use the same rapid-acting insulin analog used in the 3 months before screening.

Comparator	Glargine U100 Participants self-administered subcutaneous injections of Gla-100 at the same time each day, either morning (immediately before breakfast until lunch) or evening (immediately before the evening mela until bedtime). Injections were administered using commercially available insulin syringes. The basal insulin dose was titrated no more often than every 3 to 4 days during the first 6 weeks of each treatment period (A and B) to reach the target fasting SMPG of 80–130mg/dL (4.4–7.2mmol/L), and it was optimized by the investigators using CGM data (downloaded at the study visits). Each participant continued to use the same rapid-acting insulin analog used in the 3 months before screening.
Outcome measures	**HbA1c** • Change in HbA1c (%) **Hypoglycaemia** • Severe hypoglycaemia • Nocturnal hypoglycaemia Occurring between 0000–0559 h **Adverse events** no. of participants reporting one or more treatment- emergent AE **% time spent in target glucose range** CGM glucose range of 80–140 mg/dL (4.4–7.8 mmol/L)
Loss to follow up	Of the four participants who discontinued the study, one (1.7%) in theGla-300 group was discontinued because of pregnancy and three (5.1%) in the Gla-100 group were discontinued because of “other” non-safety-related reasons.
Methods of analysis	Data from the last 2 weeks of each 8-week treatment period (A and B) were analyzed (weeks 7–8 and weeks 15–16 combined)

Study arms

Glargine U300 (N = 30) Glargine U300 once daily (period 1) followed by glargine U100 once daily (period 2) Participants continued to use the same rapid acting insulin analog used in the 3 months before screening.
Glargine U100 (N = 29) Glargine U100 once daily (period 1) followed by glargine U300 once daily (period 2). Participants continued to use the same rapid acting insulin analog used in the 3 months before screening.

Characteristics

Arm-level characteristics

	Glargine U300 (N = 30)	Glargine U100 (N = 29)
% Female		
Sample Size	n = 13 ; % = 43.3	n = 14 ; % = 48.3
Mean age (SD)		
Mean/SD	44.9 (15.1)	43.5 (13.7)
Duration of diabetes (years)		
Mean/SD	24.1 (14.9)	20.1 (12.4)
BMI (kg/m2)		
Mean/SD	27.4 (4.9)	27.2 (5.7)
HbA1c (%)		
Mean/SD	7.51 (0.69)	7.41 (0.62)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Some concerns (No information on washout period.)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns (Open label trial and hypoglycaemia was self-reported.)
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns (No information on statistical test for carryover. Study presents the data of both periods combined.)
Overall bias and Directness	Risk of bias judgement	Some concerns (Open label trial and hypoglycaemia was self-reported. No information on statistical test for carryover. Study presents the data of both periods combined.)
	Overall Directness	Partially applicable (Study does not specify which bolus insulins were used by the participants.)

Birkeland 2011

Birkeland, 2011	
Bibliographic Reference	Birkeland, Kare I; Home, Philip D; Wendisch, Ulrich; Ratner, Robert E; Johansen, Thue; Endahl, Lars A; Lyby, Karsten; Jendle, Johan H; Roberts, Anthony P; DeVries, J Hans; Meneghini, Luigi F; Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine.; Diabetes care; 2011; vol. 34 (no. 3); 661-5

Study details

Study type	Randomised controlled trial (RCT)
Trial registration number	NCT00612040
Study location	28 centres across Australia, Germany, Norway, Sweden and the US
Study setting	Hospital setting
Study dates	Not specified
Duration of follow-up	16 weeks
Sources of funding	Study was sponsored by Novo Nordisk.
Sample size	178
Inclusion criteria	Patients aged 18-75 years of age diagnosed with type 1 diabetes ≥12 months before study, treated continually with insulin using any regimen, and having an A1C of 7.0-11.0%.
Exclusion criteria	Pregnant or breast-feeding women People with clinically significant concomitant illnesses, impaired renal and hepatic function, and a history of recurrent major hypoglycemia or of hypoglycemia unawareness.
Method of allocation	Eligible participants were randomised 1:1:1 ia a remote interactive voice/web response system to be treated with either IGlar, IDeg A or IDegB.
Intervention(s)	Degludec: Degludec (A) - Degludec U100 - 600µmol/L - 1 unit = 6 nmol Degludec (B) 900µmol/L - 1 unit = 9 nmol (data not extracted for this arm) Degludec was given in combination with aspart (U100/mL) at mealtimes. Basal insulin was administered subcutaneously, preferably in the thigh, once daily in the evening, in the period between 1h before the last main meal and bedtime, but approximately at the same time each day. Degludec was administered using a 3mL FlexPen. Apart was administered subcutaneously just before each meal, preferably in the abdominal wall. Aspart was administered using a 3mL FlexPen. Participants receiving once-daily basal insulin treatment before the study switched to trail insulin using a one-to one unit dose switch. Participants receiving twice-daily basal insulin treatment before the study were to commence trail insulin at a dose corresponding to 80% of their pretrial basal insulin dose. Based on self-measured fasting plasma glucose levels taken before breakfast, basal insulin doses were individually adjusted once a week.
Comparator	Glargine

Study type	Randomised controlled trial (RCT)
	U100/mL Glargine was given in combination with aspart (U100/mL) at mealtimes. Basal insulin was administered subcutaneously, preferably in the thigh, once daily in the evening, in the period between 1h before the last main meal and bedtime, but approximately at the same time each day. Apart was administered subcutaneously just before each meal, preferably in the abdominal wall. Aspart was administered using a 3mL FlexPen. Participants receiving once-daily basal insulin treatment before the study switched to trail insulin using a one-to one unit dose switch. Participants receiving twice-daily basal insulin treatment before the study were to commence trail insulin at a dose corresponding to 80% of their pretrial basal insulin dose. Based on self-measured fasting plasma glucose levels taken before breakfast, basal insulin doses were individually adjusted once a week.
Outcome measures	**HbA1c** • Change in HbA1c (%) **Hypoglycaemia** • Hypoglycaemia (all) • Severe hypoglycaemia Classified as: Severe - if assistance from another person was required Confirmed - if confirmed by a PG measurement of <3.1 mmol/L irrespective of any symptoms or classified as severe. • Nocturnal hypoglycaemia **Adverse events** • Serious AEs **Body weight** • Change in body weight (kg)
Loss to follow up	Degludec (A): 7 Adverse event : 2 Noncompliance: 2 Ineffective therapy: 1 Other: 2 Degludec (B): 5

Study type	Randomised controlled trial (RCT)
	Adverse event : 1 Noncompliance: 1 Ineffective therapy: 2 Other: 2 Glargine: 7 Adverse event : 1 Noncompliance: 1 Ineffective therapy: 0 Other: 5
Additional comments	Further evidence is presented in Home 2012.

Study arms

Degludec (A) (N = 59) Degludec U100 Once daily 600µmol/L - 1 unit = 6 nmol Given in combination with aspart (U100) as meal time insulin.
Degludec (B) (N = 60) Once daily 900µmol/L - 1 unit = 9 nmol Given in combination with aspart (U100) as meal time insulin. Data from this arm was not extracted as formulation has been discontinued.
Glargine (N = 59) Once daily U100/ mL Given in combination with aspart (U100) as meal time insulin.

Characteristics

Arm-level characteristics

	Degludec (A) (N = 59)	Degludec (B) (N = 60)	Glargine (N = 59)
% Female			
Sample Size	n = 22 ; % = 37	n = 23 ; % = 38	n = 27 ; % = 46
Mean age (SD)			
Mean/SD	44.5 (12.7)	45.6 (12.5)	47.2 (13.5)
BMI (kg/m²)			

	Degludec (A) (N = 59)	Degludec (B) (N = 60)	Glargine (N = 59)
Mean/SD	27.2 (3.4)	27.1 (3.6)	26.3 (3.9)
Weight (kg)			
Mean/SD	80.9 (11.8)	80.5 (14.5)	77.7 (14.2)
Diabetes duration (years)			
Mean/SD	22.7 (14.6)	20.8 (10.6)	19.1 (10.8)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

Blevins 2015

Blevins, 2015

Bibliographic Reference	Blevins, T C; Dahl, D; Rosenstock, J; Ilag, L L; Huster, W J; Zielonka, J S; Pollom, R K; Prince, M J; Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus R) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study.; Diabetes, obesity & metabolism; 2015; vol. 17 (no. 8); 726-33

Study details

Study type	Randomised controlled trial (RCT)
Trial registration number	NCT01421147.
Study location	Multinational study
Study setting	Not specified
Study dates	Not specified
Duration of follow-up	Patients received treatment for 24 weeks. Patients continued to receive their assigned treatment for an extended period of 28 weeks (total duration of 52 weeks)
Sources of funding	This study was funded by Eli Lilly and Boehringer- Ingelheim.
Sample size	535
Inclusion criteria	T1DM duration of ≥ 1 year, age ≥ 18 years, receiving basal-bolus insulin therapy for ≥ 1 year before screening, HbA1c ≤11.0% and body mass index ≤35kg/m2.
Exclusion criteria	Treatment with a biosimilar IGlar, oral antihyperglycaemic medications, recent twice-daily IGlar treatment, pramlintide, or continuous subcutaneous insulin infusion, total daily insulin dose ≥1.5 U/Kg, or ≥ episode of severe hypoglycaemia or emergency room visit or hospitalisation for poor glucose control within the past 6 months
Method of allocation	Treatment assignment was stratified by country, HbA1c value (<8.5, ≥8.5%), and time of basal insulin injection (day-time, evening/bedtime)
Intervention(s)	LY2963016 (LY IGlar) Once daily Patients started on the same dose at the same time of day as their prestudy basal insulin. At randomisation, all patients' mealtime insulins were replaced with insulin lispro at doses equivalent to their prestudy mealtime insulin, as determined by unit-to-unit conversion. Insulin dose adjustments were carried out to help patients achieve glycaemic targets [HbA1c <7%, fasting plasma glucose (FPG)≤6.0mmol/l (108mg/dl), and other preprandial capillary blood glucoses 3.9–7.2mmol/l (70–130mg/dl)], while minimizing/avoiding hypoglycaemia.
Comparator	Glargine U100 Once daily Patients started on the same dose at the same time of day as their prestudy basal insulin. At randomisation, all patients' mealtime insulins were replaced with insulin lispro at doses equivalent to their prestudy mealtime insulin, as determined by unit-to-unit conversion. Insulin dose adjustments were carried out to help patients achieve glycaemic targets [HbA1c <7%, fasting plasma glucose (FPG)≤6.0mmol/l (108mg/dl), and other preprandial capillary blood glucoses 3.9–7.2mmol/l (70–130mg/dl)], while minimizing/avoiding hypoglycaemia.

Outcome measures	**HbA1c** • Change in HbA1c (%) (24 weeks and 52 weeks) • Participants achieving HbA1c < 7% **Hypoglycaemia** • Hypoglycaemia (all) - At 24 weeks and 52 weeks • Serious hypoglycaemia - At 24 weeks and 52 weeks Hypoglycaemia was defined as blood glucose ≤ 3.9 mmol/l (≤70mg/dl) or having a sign or symptom associated with hypoglycaemia. All serious hypoglycaemic episodes were reported as serious AEs. Severe hypoglycaemia was defined as hypoglycaemic event requiring assistance of another person to actively administer treatment or other resuscitative actions. • Nocturnal hypoglycaemia Defined as any hypoglycaemic event that occurred between bedtime and waking. **Adverse events** • Adverse events - possibly related to study drug • Serious AEs • Injection site reactions **Body weight** • Change in weight (kg) **QoL** Reported in Delozier 2018
Loss to follow up	After randomisation: LY IGlar : Adverse event (2), loss to followup (1), physician decision (2), withdrawal by subject (10) IGlar : Adverse event (3), loss to followup (1), physician decision (2), withdrawal by subject (5) After 24 weeks: LY IGlar : lost to follow up (2), physician decision (1), withdrawal by subject (5) IGlar : Adverse event (2), death (1), loss to followup (5), withdrawal by subject (3)
Methods of analysis	HbA1c analyses were conducted at a central laboratory using the Variant II and Variant II turbo HbA1c testing systems.

Study arms

LY2963016 (LY IGlar) (N = 268) Once daily Lispro used a mealtime insulin
Glargine (N = 267) Glargine U100 Once daily Lispro used as mealtime insulin

Characteristics

Arm-level characteristics

	LY2963016 (LY IGlar) (N = 268)	Glargine (N = 267)
% Female		
Sample Size	n = 113 ; % = 42	n = 112 ; % = 42
Mean age (SD) (years)		
Mean/SD	41 (14)	41 (13)
BMI (kg/m²)		
Mean/SD	26 (4)	25 (4)
Body weight (kg)		
Mean/SD	76 (17)	75 (15)
Duration of diabetes (years)		
Mean/SD	16 (11)	17 (11)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Insufficient information on randomisation and allocation concealment.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Cochrane Risk of Bias Tool 2.0		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns ('Last observation carried forward' used to adjust for missing data.)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Insufficient information on randomisation and allocation concealment. Potential bias introduced due to adjustment of missing data.)
	Overall Directness	Directly applicable

Blevins 2018

Blevins, 2018

Bibliographic Reference	Blevins, Thomas C; Barve, Abhijit; Sun, Bin; Ankersen, Michael; Efficacy and safety of MYL-1501D vs insulin glargine in patients with type 1 diabetes after 52 weeks: Results of the INSTRIDE 1 phase III study.; Diabetes, obesity & metabolism; 2018; vol. 20 (no. 8); 1944-1950

Study details

Study type	Randomised controlled trial (RCT)
Trial registration number	NCT02227862
Study location	Multinational (Europe, North America, South America)
Study setting	Not specified
Study dates	Not specified
Duration of follow-up	24 weeks and 52 weeks
Sources of funding	Financial support for the study was provided by Mylan Inc. and Biocon Limited.
Sample size	558
Inclusion criteria	Established diagnosis of T1DM (according to American Diabetes Association 2014 criteria) Treated with once-daily insulin glargine for ≥ 3months, had an HbA1c ≤80 mmol/ mol (≤9.5%) at screening, aged between 18 and 65 years, had a fasting plasma C-peptide <0.3 nmol/L at screening, and had a stable weight for 3 months and a body mass index between 18.5 and 35.0 kg/m2 at screening.
Exclusion criteria	Not specified
Method of allocation	At randomisation, there was a 1:1 (unit for unit) conversion of reference glargine to MYL-1501D (100 U/mL of insulin glargine) and of pre-study mealtime insulin to insulin lispro. Stratification was carried out by region (ie, North America, Europe and South Africa) and time of insulin glargine administration (morning vs evening).
Intervention(s)	MYL-1501D (proposed glargine biosimilar) Given once daily Mealtime lispro given alongside.
Comparator	Glargine U100 Given once daily Mealtime lispro given alongside.

Outcome measures	**HbA1c** • Change in HbA1c (%) - week 24 and week 52 **Hypoglycaemia** • Hypoglycaemia (all) -Defined as SMBG 3.9 mmol/L. • Severe hypoglycaemia - Severe hypoglycaemia was considered severe if it required assistance from another person to actively administer carbohydrate, glucagon or other resuscitative actions resulting in neurological recovery, regardless of availability of a blood glucose measurement. • Nocturnal hypoglycaemia Defined as those that occurred from the time the patient went to bed at night to the time they woke up. **Adverse events** • Adverse events - no. of participants experiencing ≥ 1 treatment emergent adverse event **Body weight** • Change in body weight (kg)
Loss to follow up	In total, 41 (7.3%) patients discontinued the study before week 52, the most common reasons being protocol deviation (16/558; 2.9%) and withdrawal of consent (13/558; 2.3%). Rate of discontinuation: MYL-1501D: 6.8% Glargine: 7.9%
Additional comments	After a 4 week screening period, patients began a 6 week run-in period and were titrated with reference insulin glargine and insulin lispro as needed to ensure good diabetes control as determined by the investigator. After insulin glargine dosage was optimally titrated, insulin lispro dosage was adjusted so that patients attained a target postprandial blood glucose of 10.0 mmol/L (<180 mg/dL).

Study arms

MYL-1501D (N = 280) Once daily Given in combination with mealtime insulin lispro 3 times a day
Glargine (N = 278) Once daily Given in combination with mealtime insulin lispro 3 times a day

Characteristics

Arm-level characteristics

	MYL-1501D (N = 280)	Glargine (N = 278)
% Female		
Sample Size	n = 116 ; % = 41.4	n = 106 ; % = 38.1
Mean age (SD) (years)		
Mean/SD	42 (12)	42.2 (12)
BMI (kg/m²)		
Mean/SD	26.4 (3.7)	26.6 (4.2)
Body weight (kg)		
Mean/SD	78.9 (14.5)	80.7 (16)
Duration of diabetes (years)		
Mean/SD	18.7 (11.8)	19.7 (11.3)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Insufficient information on randomisation process.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (Unclear if results were not biased due to missing data.)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Insufficient information on randomisation process. Unclear if results were not biased due to missing data.)
	Overall Directness	Directly applicable

Bode 2013

Bode, 2013

Bibliographic Reference	Bode, B W; Buse, J B; Fisher, M; Garg, S K; Marre, M; Merker, L; Renard, E; Russell-Jones, D L; Hansen, C T; Rana, A; Heller, S R; BEGIN R Basal-Bolus Type 1 trial, investigators; Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN(R) Basal-Bolus Type 1): 2-year results of a randomized clinical trial.; Diabetic medicine : a journal of the British Diabetic Association; 2013; vol. 30 (no. 11); 1293-7

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT. Extension to Heller 2012
Study location	See Heller 2012
Study setting	See Heller 2012
Study dates	See Heller 2012
Duration of follow-up	2 years (1 year extension to the 1 year BEGIN trial)
Sources of funding	Novo Nordisk
Sample size	469 (of the 629 in year 1 of the trial)
Inclusion criteria	see Heller 2012
Method of allocation	Patients entering the extension continued their therapy for another 52 weeks with the same titration target
Intervention(s)	Degludec U100 - see Heller 2012
Comparator	Glargine U100- see Heller 2012
Outcome measures	**Hypoglycaemia** • Severe hypoglycaemia Confirmed hypoglycaemic episodes included those with a plasma glucose value of < 3.1 mmol/l or severe episodes necessitating assistance. • Nocturnal hypoglycaemia Hypoglycaemic episodes occurring from 00.01 to 05.59 h (both included) were classified as nocturnal. **Adverse events** • Adverse events • Serious adverse events • Injection site reaction
Loss to follow up	A small proportion of subjects withdrew because of adverse events [< 1% (3/351) insulin degludec; 2% (2/118) insulin glargine], hypoglycaemia [< 1% (1/351) insulin degludec; 0% (0/118) insulin glargine] or ineffective therapy [< 1% (2/351) insulin degludec; 0% (0/118) insulin glargine]. Other reasons for withdrawal were generally unrelated to safety or efficacy.
Limitations	Unclear how participants were recruited on to the extension trial.

Study arms

Degludec (N = 351) Degludec U100 Once-daily degludec with insulin aspart. 351/472 completed the extension phase of the trial
Glargine (N = 118) Glargine U100 Once-daily glargine with insulin aspart. 118/157 completed the extension phase of the trial

Characteristics

Arm-level characteristics

	Degludec (N = 351)	Glargine (N = 118)
% Female		
Sample Size	n = 141 ; % = 40.2	n = 72 ; % = 61
Mean age (SD)		
Mean/SD	43.6 (13.5)	44.6 (13.1)
BMI (kg/m²)		
Mean/SD	26.4 (3.7)	26.6 (4)
Weight (kg)		
Mean/SD	79.2 (14.3)	79.3 (15.9)
Duration of diabetes (years)		
Mean/SD	18.8 (11.7)	17.8 (11.7)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information on randomisation or allocation concealment. Study is an extension trial of Heller 2012. Unclear how patients were recruited. Study does state that those experiencing more benefit are more likley to enter the extension.)
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Cochrane Risk of Bias Tool 2.0		
interventions (effect of assignment to intervention)		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Adverse events - Open label trail.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Study is an extension trial of Heller 2012. Unclear how patients were recruited. Study does state that those experiencing more benefit are more likley to enter the extension.)
	Overall Directness	Directly applicable

Bolli 2009

Bolli, 2009

Bibliographic Reference	Bolli, G B; Songini, M; Trovati, M; Del Prato, S; Ghirlanda, G; Cordera, R; Trevisan, R; Riccardi, G; Noacco, C; Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with Type 1 diabetes.; Nutrition, metabolism, and cardiovascular diseases : NMCD; 2009; vol. 19 (no. 8); 571-9

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Italy
Study setting	21 centres
Study dates	Not reported
Duration of follow-up	30 weeks
Sources of funding	Sanofi-Aventis
Sample size	175
Inclusion criteria	Aged 18 years and above 18-60 years BMI 18-26 mg/kg² History of Type 1 diabetes For more than 3 years Treated on a basal-bolus insulin regimen Intensive insulin therapy (NPH twice or more daily and lispro or regular human insulin at mealtimes) HbA1c 7 - 9%
Intervention(s)	Glargine U100 Glargine (Lantus, Sanofie Aventis) once daily at dinnertime by means of pen device (OptiPen pro 1). Dinnertime glargine was titrated to achieve a fasting blood glucose target value 90-120 mg/dL, but avoiding nocturnal hypoglycaemia. The dose of lispro was adjusted to a target post-prandial blood glucose of <140 mg/dL. Additional doses (1 or 2 U) of lispro were used to correct unexpected hyperglycaemia
Comparator	NPH (Humulin I, Eli Lilly and Co.) twice (or more) daily (bedtime and lunchtime) by pen (Humapen Lilly). Bedtime NPH was titrated to achieve a fasting blood glucose target value 90-120 mg/dL, but avoiding nocturnal hypoglycaemia. The lunchtime dose of NPH was adjusted to a target predinner blood glucose 90-120 mg/dl. Lispro doses matched those in the glargine arm Within the NPH group, 62 patients were on NPH twice daily, 10 were on three times daily and 2 were on NPH four times daily.

Outcome measures	**HbA1c** • Change in HbA1c (%) **Hypoglycaemia** • Hypoglycaemia (all) - Change in hypoglycaemia (episodes/ patient/ month). • Serious hypoglycaemia - Change in serious hypoglycaemia (episode/ patient/ month) Hypoglycaemia was defined as BG ≤72 mg/mL and included the total number of diurnal and nocturnal hypoglycaemia that occurred. Serious hypoglycaemia was defined as an event with BG < 42 mg/dL. Severe hypoglycaemia an event with symptoms consistent with hypoglycaemia, during which the participant required the assistance of another person, or with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. • Nocturnal hypoglycaemia Change in severe nocturnal hypoglycaemia Serious nocturnal hypoglycaemia was defined as BG < 42 mg/mL and occurring between bedtime and before getting up in the morning. **Adverse events** • Adverse events- related to study drug • Serious AEs **QoL** • Measured using the Well-Being Enquiry for Diabetics (WED) questionnaire at the randomisation visit (week 0), at week 12 and at week 24. WED is a 50- item questionnaire providing an evaluation of 5 aspects of quality life: symptoms, discomfort, serenity and impact.
Loss to follow up	Glargine arm: 7 drop outs - Criteria violations (4), protocol violations (2), consent withdrawn (1) Degludec arm: 12 drop outs - Criteria violations (3), protocol violations (1), consent withdrawn (3), poor compliance (2), lost to follow uo (1), no efficiacy (1)
Additional comments	Study included a 4 week ruin-in phase. Within the NPH group, 62 patients were on NPH twice daily, 10 were on three times daily and two were on NPH four times daily.

Study arms

Glargine (N = 85) Glargine U100 Once daily glargine with lispro
NPH (N = 90) Twice daily (or more) NPH with lispro

Characteristics

Arm-level characteristics

	Glargine (N = 85)	NPH (N = 90)
HbA1c (%)		
Mean/SD	7.82 (0.68)	7.82 (0.63)
% Female		
Nominal	43.5	45.5
Age (years)		
Mean/SD	35.5 (10.6)	37 (9.4)
BMI (kg/m²)		
Mean/SD	23.3 (2)	23.6 (1.9)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation and allocation concealment)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Quality of life outcomes were subjective and participants were aware of the intervention they were assigned to)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information and allocation concealment. Quality of

Cochrane Risk of Bias Tool 2.0		
		life and AEs outcomes were subjective and the trial was open label)
	Overall Directness	Indirectly applicable (NPH was given twice daily or more.)

Chatterjee 2007

Chatterjee, 2007

Bibliographic Reference	Chatterjee, S; Jarvis-Kay, J; Rengarajan, T; Lawrence, I G; McNally, P G; Davies, M J; Glargine versus NPH insulin: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes--the glargine and aspart study (GLASS) a randomised cross-over study.; Diabetes research and clinical practice; 2007; vol. 77 (no. 2); 215-22

Study details

Study type	Crossover randomised controlled trial
Study location	UK
Study setting	Single centre
Study dates	Not reported
Duration of follow-up	16 weeks
Sources of funding	Novo Nordisk and Aventis
Sample size	60
Inclusion criteria	Aged 18 years and above 18-75 years BMI <45 kg/m² History of Type 1 diabetes And on insulin for at least 6 months HbA1c 6-11%
Method of allocation	Subjects completed a 4-week run-in period during which they received thrice-daily pre-prandial insulin aspart and twice-daily NPH. Subsequently, they were allocated to receive insulin aspart in combination with either once-daily insulin glargine or twice-daily NPH. Allocation was based on opening consecutively numbered sealed envelopes in which the name of the basal insulin had previously been randomly inserted. Insulin glargine or NPH was continued for 16 weeks before crossing over to the other basal insulin. The number of units of insulin equal to that administered at the end of the first treatment period was prescribed, unless previous home glucose monitoring suggested a dosage modification. On switching from glargine to NPH, the current basal dose of insulin was increased by 20% to compensate for switching from a once-daily basal regimen to a twice-daily basal regimen. Conversely, when switching from NPH to glargine, the basal dose of insulin was reduced by 20%.
Intervention(s)	Insulin glargine (Lantus, Aventis Pharma, Frankfurt, Germany) as a once-daily basal insulin (at bedtime) in combination with the rapid-acting analogue insulin aspart (Novorapid, Novo Nordisk) in a basal bolus regimen. Glargine was administered using the Optipen1 Pro 1 injection device (Aventis) and the Novopen1 3 (Novo Nordisk) was used to administer insulin aspart. Glargine was continued for 16 weeks before crossing over to NPH. Blood glucose targets were: 4–6.7 mmol/L before meals, 4–8 mmol/L at bedtime and <8 mmol/L 2 h after main meals

Comparator	NPH insulin (Insulatard1, Novo Nordisk, Crawley, West Sussex, UK) as a twice-daily basal insulin, in combination with the rapid-acting analogue insulin aspart (Novorapid1, Novo Nordisk) in a basal bolus regimen. The Novopen1 3 (Novo Nordisk) was used to administer NPH and insulin aspart. NPH was continued for 16 weeks before crossing over to glargine. Blood glucose targets were: 4–6.7 mmol/L before meals, 4–8 mmol/L at bedtime and <8 mmol/L 2 h after main meals
Outcome measures	**HbA1c** • Change in HbA1c (%) - Calculated using baseline and follow up data. **Hypoglycaemia** • Severe hypoglycaemia Defined as a hypoglycaemic episode requiring third-party assistance and/or intravenous glucose or intramuscular glucagon. **Body weight** • Change in weight (kg)

Study arms

Glargine (N = 25) Glargine U100 Once-daily glargine (period 1) followed by twice-daily NPH (period 2). Both basal insulins were given in combination with insulin aspart
NPH (N = 33) Twice-daily NPH (period 1) followed by once-daily glargine (period 2). Both basal insulins were given in combination with insulin aspart

Characteristics

Study-level characteristics

	Study (N = 60)
% Female	
Nominal	41.6
Mean age (SD)	
Mean/SD	42.9 (12.5)
BMI (kg/m²)	
Mean/SD	27 (4.2)
HbA1c (%)	
Mean/SD	8.53 (1.15)

Cochrane Risk of Bias Tool 2.0 Crossover trial		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Baseline characteristics not reported for each arm)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Some concerns (No washout period)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns (No information about a statistical test for carry-over)
Overall bias and Directness	Risk of bias judgement	Some concerns (Baseline characteristics not reported for each arm, no washout period and no information about a statistical test for carry-over.)
	Overall Directness	Directly applicable

Davies 2014

Davies, 2014

Bibliographic Reference	Davies, M J; Gross, J L; Ono, Y; Sasaki, T; Bantwal, G; Gall, M A; Niemeyer, M; Seino, H; BEGIN BB T1 Study, Group; Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial.; Diabetes, obesity & metabolism; 2014; vol. 16 (no. 10); 922-30

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Brazil, Finland, India, Italy, Japan, Macedonia, UK
Study setting	Clincal sites
Study dates	February - December 2010
Duration of follow-up	26 weeks
Sources of funding	Novo Nordisk
Sample size	456
Inclusion criteria	Aged 18 years and above 20 years and over for Japan BMI ≤35.0 kg/m² History of Type 1 diabetes For at least 12 months Treated on a basal-bolus insulin regimen For at least 12 months HbA1c ≤10%
Exclusion criteria	Recurrent major hypoglycaemia Impaired hepatic or renal function Hypoglycaemic unawareness Cardiovascular disease For 6 months prior to the trial
Method of allocation	Eligible participants were randomised 2:1 to either OD IDeg or OD IDet as basal insulin, both in combination with mealtime IAsp. For randomisation, an interactive voice/web response system with centralised block randomisation was used.
Intervention(s)	Once-daily degludec (Tresiba®, 100 U/ml) as basal insulin, in combination with mealtime insulin aspart (NovoRapid® 100 U/ml). Both were injected subcutaneously using a 3-ml FlexPen® (NovoNordisk). Basal insulin was titrated individually once a week to a plasma glucose target of 3.9–4.9 mmol/l. Aspart was given at an equivalent dose to participant's pre-trial bolus insulin dose
Comparator	Once-daily detemir (Levemir®, 100 U/ml) as basal insulin, in combination with mealtime insulin aspart (NovoRapid® 100 U/ml). Both were injected subcutaneously using a 3-ml FlexPen® (NovoNordisk). Plasma glucose targets and bolus insulin doses were the same as those used in the degludec arm

Outcome measures	**HbA1c** • Change in HbA1c (%) • proportion of participants with HbA1c <7.0% **Hypoglycaemia** • Hypoglycaemia (all) Defined as PG< 3.1 mmol/l, regardless of symptoms or severe episodes (requiring assistance from another person). • Severe hypoglycaemia • Nocturnal hypoglycaemia nocturnal hypoglycaemia defined as onset between 00:01 and 05:59 hours. **Adverse events** • Adverse events - no. of participants with AEs possibly or probably related to investigational product • Serious adverse events - no. of patients with serious AEs • Injection site reactions **Body weight** • Change in body weight (kg)
Loss to follow up	Degludec arm - 18 withdrawn: adverse event (3), non-compliance (3), ineffective therapy (0), withdrawal criteria (6), other (6) Detemir arm - 14 withdrawn: adverse event (1), non-compliance (4), ineffective therapy (2), withdrawal criteria (3), other (4)

Study arms

Degludec (N = 303) Degludec U100 Once-daily insulin degludec with mealtime insulin aspart
Detemir (N = 153) Once-daily insulin detemir with mealtime insulin aspart

Characteristics

Arm-level characteristics

	Degludec (N = 303)	Detemir (N = 153)
% Female		
Nominal	50.3	43.8
Age (years)		

	Degludec (N = 303)	Detemir (N = 153)
Mean/SD	41.1 (14.9)	41.7 (14.4)
BMI (kg/m²)		
Mean/SD	24 (3.5)	23.7 (3.4)
HbA1c (%)		
Mean/SD	8 (1)	8 (0.9)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Low for HbA1c and hypoglycaemia. Some concerns for adverse events - may have been participant reported and trial was open label)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Low for HbA1c and hypoglycaemia. Some concerns for adverse events - may have been participant reported and trial was open label)
	Overall Directness	Directly applicable

De Leeuw 2005

De Leeuw, 2005

Bibliographic Reference	De Leeuw, I; Vague, P; Selam, J-L; Skeie, S; Lang, H; Draeger, E; Elte, J W F; Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin.; Diabetes, obesity & metabolism; 2005; vol. 7 (no. 1); 73-82

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Europe (countries not reported)
Study setting	42 sites
Study dates	12 months (dates not reported)
Duration of follow-up	12 months (initially 6 months followed by a 6 month extension phase)
Sources of funding	Novo Nordisk A/S, Denmark
Sample size	425
Inclusion criteria	Aged 18 years and above BMI 35 kg/m² History of Type 1 diabetes For 1 year Treated on a basal-bolus insulin regimen For at least 2 months Caucasian patients HbA1c 12% Total daily basal insulin requirement of 100 IU/day
Exclusion criteria	Proliferative retinopathy or maculopathy Recurrent major hypoglycaemia Allergy to insulin Pregnant or breast-feeding women Impaired hepatic or renal function Severe cardiac problems Uncontrolled hypertension
Intervention(s)	Insulin detemir (1200 nmol/ml; 1U¼24 nmol) subcutaneously before breakfast and bedtime, and aspart (100 U/ml, NovoRapid, Novo Nordisk) before each main meal, using the NovoPen 3 device (Novo Nordisk). Doses were adjusted aiming at a glycaemic target of 4–7 mmol/l for fasting blood glucose, preprandial and early morning blood glucose. Postprandial glycaemic target was <10 mmol/l 90 min after a meal
Comparator	NPH insulin (Isophane human insulin 100 IU/ml, Novo Nordisk, Bagsvaerd, Denmark) subcutaneously before breakfast and bedtime, and aspart (100 U/ml, NovoRapid, Novo Nordisk) before each main meal. Method of delivery and blood glucose targets matched those for the detemir arm

Outcome measures	**HbA1c** • Change in HbA1c (%)- calculate using baseline and follow up data **Hypoglycaemia** • Major hypoglycaemia (no. of patients) An episode with severe central nervous system symptoms consistent with hypoglycaemia, in which the subject was unable to treat himself/herself and which had one of the following characteristics: BG recorded as <2.8 mmol/l or symptom reversal achieved with food, glucose or glucagon], minor (BG recorded as <2.8 mmol/l, but the patient managed the episode unaided) and as symptoms only (symptomatic episodes not requiring assistance and not confirmed by a BG measurement). • Nocturnal hypoglycaemia If hypoglycaemia occurred within the time interval 23:00-06:00. **Adverse events** • Serious AEs - probably/ possibly related to study medication • Injection site reactions **Body weight** • Change in weight (kg)- calculated
Loss to follow up	1 (detemir group) Three patients withdrew from the NPH insulin group, due to 'ineffective therapy', 'noncompliance' and 'other reasons'. Five patients withdrew from the insulin detemir group, one due to noncompliance, two due to AEs and two due to 'other reasons'.
Limitations	Study states that the cohort that continued into the extension phase cannot be considered randomized, as their inclusion was voluntary.

Study arms

Detemir (N = 216) Twice-daily insulin detemir with mealtime aspart
NPH (N = 99) Twice-daily NPH insulin with mealtime aspart

Characteristics

Arm-level characteristics

	Detemir (N = 216)	NPH (N = 99)
% Female		
Nominal	46.3	47.5
Age (years)		
Mean/SD	40.1 (12.8)	40.8 (13.2)
BMI (kg/m²)		
Mean/SD	24.4 (2.9)	24.6 (3.5)
HbA1c (%)		
Mean/SD	8.18 (1.14)	8.03 (1.11)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High (No information on allocation concealment or randomisation process. Additionally after initial 6 months of the trial, there was a 6 month extension phase which was voluntary.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (May not have been possible to blind participants to interventions.)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Outcome hypoglycaemia- Study states that it is possible that as risk estimates of hypoglycaemia were based on self recording by patients, those receiving insulin detemir were more diligent in their reporting.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High (No information on allocation concealment or randomisation process. Additionally

Cochrane Risk of Bias Tool 2.0		
		after initial 6 months of the trial, there was a 6 month extension phase which was voluntary. Hypoglycaemia- open label trial. Hypoglycaemia was self-reported.)
	Overall Directness	Directly applicable

DeLozier 2018

DeLozier, 2018

Bibliographic Reference	DeLozier, A.M.; Ilag, L.L.; Perez-Nieves, M.; Kaushik, P.; Duan, R.; Pollom, R.K.; Kabul, S.; Patient-reported outcome measures in phase III trials of LY2963016 insulin glargine and reference insulin glargine products: ELEMENT 1 and ELEMENT 2; GaBI Journal; 2018; vol. 7 (no. 2); 6

Study details

Study type	Randomised controlled trial (RCT) Presents patient reported outcomes from Blevins 2015
Trial registration number	See Blevins 2015
Study location	See Blevins 2015
Study setting	See Blevins 2015
Study dates	See Blevins 2015
Duration of follow-up	See Blevins 2015
Sources of funding	See Blevins 2015
Sample size	535
Inclusion criteria	T1DM duration of ≥ 1 year, age ≥ 18 years, receiving basal-bolus insulin therapy for ≥ 1 year before screening, HbA1c ≤11.0% and body mass index ≤35kg/m2.
Exclusion criteria	Treatment with a biosimilar IGlar, oral antihyperglycaemic medications, recent twice-daily IGlar treatment, pramlintide, or continuous subcutaneous insulin infusion, total daily insulin dose ≥1.5 U/Kg, or ≥ episode of severe hypoglycaemia or emergency room visit or hospitalisation for poor glucose control within the past 6 months
Method of allocation	See Blevins 2015
Intervention(s)	LY2963016 (LY IGlar) See Blevins 2015
Comparator	Glargine See Blevins 2015
Outcome measures	**QoL** • Insulin treatment satisfaction questionnaire (ITSQ)- Change in total score - score was transformed (which means increases are improvements). Measures inconvenience of regimen and hypoglycaemia. • Adult low blood sugar survey (ALBSS) -Change in total score - total score (decreases are improvements). Measures fear or worry of hypoglycaemic events associated with insulin therapy and subsequent behaviours associated with avoiding future events.
Methods of analysis	Treatment satisfaction related to insulin therapy was assessed using the Insulin Treatment Satisfaction Questionnaire and Adult Low Blood Sugar Survey. All individual patient domain scores were calculated at baseline, 24 weeks and end-point using the non-missing items.

Study arms

LY IGlar (N = 268) See Blevins 2015
Glargine (N = 267) See Blevins 2015

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Insufficient information on randomisation and allocation concealment.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open label trial. Potential bias introduced for subjective outcomes.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Open label trial. Potential bias introduced for subjective outcomes.)
	Overall Directness	Directly applicable

Fulcher 2005

Fulcher, 2005

Bibliographic Reference	Fulcher, G R; Gilbert, R E; Yue, D K; Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy.; Internal medicine journal; 2005; vol. 35 (no. 9); 536-42

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Australia
Study setting	9 centres
Study dates	November 2000 - November 2001
Duration of follow-up	30 weeks
Sources of funding	Aventis
Sample size	125
Inclusion criteria	Aged 18 years and above 18-80 years History of Type 1 diabetes Treated with insulin for at least 1 year HbA1c ≥8%
Exclusion criteria	Impaired hepatic or renal function Night shift workers
Intervention(s)	Once-daily insulin glargine as basal insulin, given at 10 pm, using the OptiPen Pro. Used in combination with preprandial insulin lispro three times per day. Blood glucose targets: fasting = 5.5 mmol/L, preprandial 3.9–6.7 mmol/L, 2-h postprandial <8 mmol/L and 3 AM >3.6 mmol/L
Comparator	Once-daily NPH insulin as basal insulin, given at 10 pm, using the OptiPen Pro. Used in combination with preprandial insulin lispro three times per day. Blood glucose targets were the same as those for the glargine arm
Outcome measures	**Hypoglycaemia** • Hypoglycaemia (all) Defined as an event with symptoms consistent with hypoglycaemia that was mild (2.8–3.6 mmol/L), moderate (<2.8 mmol/L) or severe • Nocturnal hypoglycaemia Defined as symptoms of hypoglycaemia occurring after the evening insulin injection and before the morning insulin dose. **Adverse events** • Adverse events • Serious AEs • Injection site reactions

Loss to follow up	Eighteen patients (14.4%) withdrew from the study, more from the NPH group than from the glargine group (14 (22.2%) versus four patients (6.4%)). Reasons for withdrawal were patient request (seven patients (5.6%)), non-compliance (four patients (3.2%)), personal reasons (three patients (2.4%)), and dislike of the titration regimen and/or the study requirements (two patients (1.6%)).
Methods of analysis	More patients withdrew from the NPH group than from the glargine group.
Additional comments	Study included a 2 week screening period which involved patients to continue on previous regimen

Study arms

Glargine (N = 62) Glargine U100 Once-daily insulin glargine with three-times daily insulin lispro
NPH (N = 63) Once-daily NPH insulin with three-times daily insulin lispro

Characteristics

Arm-level characteristics

	Glargine (N = 62)	NPH (N = 63)
% Female		
Nominal	61.3	60.3
Age (years)		
Mean/SD	41.6 (12.9)	39.3 (13.9)
BMI (kg/m²)		
Mean/SD	27 (3.6)	26 (3.9)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information about blinding or allocation concealment)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Cochrane Risk of Bias Tool 2.0		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High (22% withdrew from the NPH arm compared to 6% from the glargine arm)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High (No information about randomisation or allocation concealment. Much higher % (22%) withdrew from the NPH arm than the glargine arm (6%))
	Overall Directness	Directly applicable

Heise 2012

Heise, 2012

Bibliographic Reference	Heise, T; Hermanski, L; Nosek, L; Feldman, A; Rasmussen, S; Haahr, H; Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes.; Diabetes, obesity & metabolism; 2012; vol. 14 (no. 9); 859-64

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Germany
Study setting	1 site
Study dates	Not reported
Duration of follow-up	12 days
Sources of funding	Novo Nordisk
Sample size	54
Inclusion criteria	Aged 18 years and above 18-65 BMI 18.0-28.0 kg/m² History of Type 1 diabetes For a minimum of 12 months Treated on a basal-bolus insulin regimen treated with multiple daily insulin injections ≥12 months (total daily insulin <1.2 U/kg/day and daily basal insulin ≥0.2 U/kg/day) HbA1c ≤10.0%
Exclusion criteria	Recurrent major hypoglycaemia Pregnant or breast-feeding women Hypoglycaemic unawareness
Method of allocation	Not specified.
Intervention(s)	Degludec U100 0.4 U/kg body weight of degludec (100 U/ml; Novo Nordisk, Bagsvaerd, Denmark) once daily for 12 days. Basal insulin was administered by subcutaneous injection into a lifted skin fold in the thigh. All injections were done at approximately 20:00 hours and performed with a syringe by a person otherwise not involved in the study. Patients self-administered bolus injections of insulin aspart for prandial glucose control
Comparator	Glargine U100 0.4 U/kg body weight of glargine (Lantus, 100 IU/ml; Sanofi, Frankfurt, Germany) once daily for 12 days. Basal insulin was administered by subcutaneous injection into a lifted skin fold in the thigh. All injections were done at approximately 20:00 hours and performed with a syringe by a person otherwise not involved in the study. Patients self-administered bolus injections of insulin aspart for prandial glucose control

Outcome measures	**Hypoglycaemia** Serious hypoglycaemia Hypoglycaemic was defined as rates of self-reported confirmed hypoglycaemia (plasma glucose <56mg/dl [3.1 mmol/l] or severe hypoglycaemia requiring assistance) Nocturnal hypoglycaemia Occurring between 00:01 and 05:59 hours. **Adverse events** Serious adverse events Injection site reactions
Loss to follow up	Two subjects in the IDeg group withdrew consent; one subject withdrew on day 5 before the first clamp and one subject withdrew after the first clamp.

Study arms

Degludec (N = 25) Degludec U100 Degludec once daily for 12 days with bolus insulin aspart
Glargine (N = 27) Glargine U100 Glargine once daily for 12 days with bolus insulin aspart

Characteristics

Arm-level characteristics

	Degludec (N = 25)	Glargine (N = 27)
% Female		
Nominal	15	7
Age (years)		
Nominal	40	36
BMI (kg/m²)		
Mean/SD	24.6 (2.4)	24.8 (2)

	Degludec (N = 25)	Glargine (N = 27)
HbA1c (%)		
Mean/SD	7.8 (1.1)	7.5 (0.8)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation and allocation concealment)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information about randomisation and allocation concealement)
	Overall Directness	Directly applicable

Heise 2017

Heise, 2017

Bibliographic Reference	Heise, Tim; Norskov, Marianne; Nosek, Leszek; Kaplan, Kadriye; Famulla, Susanne; Haahr, Hanne L; Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes.; Diabetes, obesity & metabolism; 2017; vol. 19 (no. 7); 1032-1039

Study details

Study type	Crossover randomised controlled trial
Study location	Germany
Study setting	1 centre
Study dates	August 2015 - April 2016
Duration of follow-up	12 days
Sources of funding	Novo Nordisk
Sample size	60
Inclusion criteria	Aged 18 years and above 18-64 years old BMI 18.5-29.0 kg.m² HbA1c <9.0% Multiple daily insulin injections or continuous s.c. insulin infusion for ≥12 months (total daily insulin <1.2 U/kg/d) and a daily basal insulin requirement ≥0.2 U/kg/d
Exclusion criteria	Recurrent major hypoglycaemia Hypoglycaemic unawareness
Intervention(s)	Degludec U200 0.4 U/kg of insulin degludec 200 U/mL (Tresiba; Novo Nordisk, Bagsvaerd, Denmark) once daily for 12 days (first treatment period), followed by a complete crossover to glargine U300 (Toujeo; Sanofi, Frankfurt, Germany) during the second treatment period. Insulin aspart was given as bolus insulin. Treatment periods were separated by a wash-out period lasting 7 to 21 days
Comparator	Glargine U300 0.4 U/kg of glargine U300 (Toujeo; Sanofi, Frankfurt, Germany) once daily for 12 days (first treatment period), followed by a complete crossover to insulin degludec 200 U/mL (Tresiba; Novo Nordisk, Bagsvaerd, Denmark) during the second treatment period. Insulin aspart was given as bolus insulin.. Treatment periods were separated by a wash-out period lasting 7 to 21 days

Outcome measures	**Hypoglycaemia** Hypoglycaemia (all) Severe hypoglycaemia Hypoglycaemia episodeswere defined as confirmed when they were either “severe”, asper the American Diabetes Association classification,10 or verified byplasma glucose levels <3.1 mmol/L (56 mg/dL). **Adverse events** Adverse events Serious AEs
Loss to follow up	During the first treatment period, 3 participants (IDeg, n = 2; IGlar-U300, n = 1) discontinued as a result of investigator decision (low HbA1c and several hypoglycaemic episodes), withdrawal of consent and protocol violation (dose miscalculated by site personnel), respectively.
Additional comments	The treatment periods were separated by a wash-out period lasting 7 to 21 days to ensure that there were no carryover effects from the previous period.

Study arms

Degludec (N = 30) Degludec U200 0.4 U/kg Insulin degludec once daily for 12 days (period 1), followed by a complete crossover to insulin glargine-U300 once daily for 12 days (period 2)
Glargine (N = 30) Glargine U300 0.4 U/kg Insulin glargine-U300 once daily for 12 days (period 1), followed by a complete crossover to insulin degludec once daily for 12 days (period 2)

Characteristics

Study-level characteristics

	Study (N =)
Mean age (SD)	
Mean/SD	45.1 (empty data)
BMI (kg/m²)	
Mean/SD	25.6 (empty data)
HbA1c (%)	
Mean/SD	7.3 (empty data)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation and allocation concealement. No baseline characteristics for each arm)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information about randomisation, allocation concealement and baseline characteristics.)
	Overall Directness	Directly applicable

Heller 2012

Heller, 2012	
Bibliographic Reference	Heller, Simon; Buse, John; Fisher, Miles; Garg, Satish; Marre, Michel; Merker, Ludwig; Renard, Eric; Russell-Jones, David; Philotheou, Areti; Francisco, Ann Marie Ocampo; Pei, Huiling; Bode, Bruce; BEGIN Basal-Bolus Type 1 Trial, Investigators; Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial.; Lancet (London, England); 2012; vol. 379 (no. 9825); 1489-97

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	France, Germany, Russia, South Africa, UK, USA
Study setting	79 sites
Study dates	September 2009 - November 2010
Duration of follow-up	52 weeks
Sample size	629
Inclusion criteria	Aged 18 years and above BMI ≤35 kg/m² History of Type 1 diabetes For at least 1 year Treated on a basal-bolus insulin regimen For at least 1 year HbA1c ≤10%
Exclusion criteria	Not reported
Method of allocation	Eligible participants were randomly assigned in a 3:1 ratio to once daily insulin degludec or insulin glargine, by means of a central interactive voice or web response system. The random allocation scheme was computer generated using blocks.
Intervention(s)	Degludec U100 Once-daily insulin degludec (100 U/mL, subcutaneously, 3 mL FlexPen, insulin and insulin pen manufactured by Novo Nordisk, Bagsværd, Denmark) in combination with meal-time insulin aspart (NovoRapid/NovoLog, 100 U/mL, subcutaneously, 3 mL FlexPen, Novo Nordisk, Bagsvaerd, Denmark). Basal insulin dose was titrated with the aim of achieving before-breakfast plasma glucose concentration of 3·9 - 5·0 mmol/L. Bolus insulin doses were titrated with the aim of achieving preprandial (of next meal) and bedtime plasma glucose concentrations of 3·9 - 5·0 mmol/L
Comparator	Glargine U100 Once-daily insulin glargine (Lantus, 100 U/mL, subcutaneously, 3 mL SoloStar, insulin and insulin pen manufactured by Sanofi , Paris, France), in combination with meal-time insulin aspart (NovoRapid/NovoLog, 100 U/mL, subcutaneously, 3 mL FlexPen, Novo Nordisk, Bagsvaerd, Denmark). Basal insulin dose was titrated with the aim of achieving before-breakfast plasma glucose concentration of 3·9 - 5·0 mmol/L. Bolus insulin doses were titrated with the aim of achieving preprandial (of next meal) and bedtime plasma glucose concentrations of 3·9 - 5·0 mmol/L

Outcome measures	**HbA1c** Change in HbA1c (%) Patients achieving HbA1c target (<7%, <53 mmol/mol) **Hypoglycaemia** Confirmed hypoglycaemia (all) - plasma glucose concentration less than 3.1 mmol/L Severe hypoglycaemia - no. of participants - necessitating assistance Nocturnal hypoglycaemia Occurring from 0001h and 0559h **Adverse events** Adverse events possibly or probably related to basal insulin Serious AEs Injection site reactions **Body weight** Change in weight (kg)

Study arms

Degludec (N = 472) Degludec U100 Insulin degludec once daily, in combination with mealtime insulin aspart
Glargine (N = 157) Glargine U100 Insulin glargine once daily, in combination with mealtime insulin aspart

Characteristics

Arm-level characteristics

	Degludec (N = 472)	Glargine (N = 157)
% Female		
Nominal	41	43
Age (years)		
Mean/SD	42.8 (13.7)	43.7 (13.3)
BMI (kg/m²)		
Mean/SD	26.3 (3.7)	26.4 (4.2)

	Degludec (N = 472)	Glargine (N = 157)
HbA1c (%)		
Mean/SD	7.7 (0.9)	7.7 (1)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low (For objective trials Moderate - adverse events)
	Overall Directness	Directly applicable

Heller 2009

Heller, 2009

Bibliographic Reference	Heller, Simon; Koenen, Christoph; Bode, Bruce; Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial.; Clinical therapeutics; 2009; vol. 31 (no. 10); 2086-97

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Multinational
Study setting	Trial sites
Study dates	Not reported
Duration of follow-up	52 weeks
Sources of funding	Novo Nordisk
Sample size	443
Inclusion criteria	Aged 18 years and above HbA1c ≤11.0% Treated on a basal-bolus insulin regimen For at least 3 months
Exclusion criteria	Proliferative retinopathy or maculopathy Recurrent major hypoglycaemia Impaired hepatic or renal function Severe cardiac problems Uncontrolled hypertension
Intervention(s)	Once or twice daily Once daily (in the evening) insulin detemir with mealtime insulin aspart. If pretrial basal insulin had been used once daily then patients were transferred to the same number of units as the equivalent basal insulin dose. If pretrial basal insulin had been administered more frequently, the total daily basal insulin dose was reduced by 30% and given once daily, followed by dose titration. Plasma glucose target was ≤6.0 mmol/L (≤108 mg/dL) before breakfast and dinner, with no episodes of significant hypoglycaemia. Mealtime insulin was adjusted to achieve a 90-minute postprandial PG target of ≤9.0 mmol/L. If patients in the detemir arm were achieving the PG target (≤6.0 mmol/L (≤108 mg/dL)) before breakfast but not before dinner, a second daily dose (initially 4 U) administered in the morning was added to the usual evening dose.
Comparator	Glargine U100 Once daily In the glargine arm, the dose was administered once daily regardless of the predinner PG measurement, in accordance with its FDA-approved labelling.

Outcome measures	**HbA1c** Change in HbA1c (%) - calculated using baseline and follow up data Achieved an HbA1c value ≤ 7% **Hypoglycaemia** Hypoglycaemic episodes were defined as major (the patient could not treat the episode by himself/herself), minor (the patient could treat himself/herself and the measured PG value was <3.1 mmol/L), or symptoms only (the patient could treat himself/herself and no PG measurement was taken or the measured PG value was ≥3.1 mmol/L). Hypoglycaemia (all) Major hypoglycaemia Nocturnal hypoglycaemia Occurring from 11 pm up to but not including 6 am. **Adverse events** Adverse events Serious adverse events (possibly/probably related to basal insulin) Injection site reactions **Body weight** Change in body weight (kg)
Loss to follow up	The primary reasons for withdrawal in the detemir group were noncompliance with the protocol (15 [5.0%]), as determined by the patient's physician, and other reasons (10 [3.3%]) that included gastroparesis, withdrawal of consent, weight gain, relocation, recommencement of the pretrial regimen, and incorrect dispensing of study drug. The most common reason for noncompliance that was considered likely to have a potential impact on patient outcomes was >3 consecutive days without study medication in the last 8 weeks of the trial (7 patients in the detemir group, 1 in the glargine group). The most common reasons for withdrawal in the glargine group were ineffective therapy (5 [5%]) and other reasons (12 [8.2%]) that included incorrect dispensing of study drug, off-label use of glargine (twice daily), patient's perception that the study was too time consuming, patient's decision not to continue glargine, patient's dissatisfaction with treatment, withdrawal of consent, and pregnancy.
Additional comments	After 52 weeks of treatment, 90 (34.2%) of 263 completing patients were receiving once-daily detemir and 173 (65.8%) were receiving twice-daily detemir. Although the protocol specified once-daily administration of glargine, 7 patients (4.8%) in that group moved to a twice-daily regimen at some time during the trial.

Study arms

Detemir (N = 299) Once-daily or twice daily insulin detemir with mealtime insulin aspart
Glargine (N = 144) Once-daily insulin glargine with mealtime insulin aspart

Characteristics

Arm-level characteristics

	Detemir (N = 299)	Glargine (N = 144)
% Female		
Nominal	44.1	43.8
Age (years)		
Mean/SD	42 (13)	41 (12)
BMI (kg/m²)		
Mean/SD	26.5 (4)	26.3 (3.9)
HbA1c (%)		
Mean/SD	8.1 (1.1)	8.1 (1.2)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Participants were assigned to once daily glargine however physicians chose to split the glargine dose, adminstering it twice daily in contravention of the approved labeling. Study states that they participants could have introduced bias into the glargine data set.)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Cochrane Risk of Bias Tool 2.0		
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Low for HbA1c. Some concerns for adverse events and hypoglycaemic outcomes - may have been a participant-reported outcome and the trial is open label)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Deviation from protocol. Adverse events may have been a participant-reported outcome and the trial is open label.)
	Overall Directness	Directly applicable

Hermansen 2001

Hermansen, 2001

Bibliographic Reference	Hermansen, K; Madsbad, S; Perrild, H; Kristensen, A; Axelsen, M; Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy.; Diabetes care; 2001; vol. 24 (no. 2); 296-301

Study details

Study type	Randomised controlled trial (RCT) Crossover trial
Study location	Denmark
Study setting	7 sites
Study dates	2 6-week treatment periods (dates not reported)
Duration of follow-up	6 weeks
Sources of funding	Novo Nordisk A/S, Denmark
Sample size	59
Inclusion criteria	Aged 18 years and above 18 - 55 years BMI <27.5 kg/m² History of Type 1 diabetes For over 2 years Treated on a basal-bolus insulin regimen NPH with human soluble insulin for at least 6 months Caucasian patients HbA1c ≤8.7% Glucagon-stimulated C-peptide ≤0.1 nmol/l NPH dose <40 IU/day

Exclusion criteria	Proliferative retinopathy or maculopathy Recurrent major hypoglycaemia Allergy to insulin Pregnant or breast-feeding women Impaired hepatic or renal function decompensated heart failure; unstable angina pectoris; myocardial Severe cardiac problems decompensated heart failure; unstable angina pectoris; myocardial infarction within the last year; hypertension (systolic and/or diastolic blood pressure ≥180 and 100 mmHg, respectively) Hypoglycaemic unawareness Alcohol or narcotics abuse
Intervention(s)	Insulin detemir (100 U/ml, 100 U = 600 nmol) between 21:00 and 23:00 and HSI (Actrapid 100 IU/ml, Novo Nordisk A/S) 30 min before each main meal as subcutaneous injections. Meal-related insulin was administered in the abdominal region and basal insulin in the thigh with a NovoPen 1.5 device (One Touch II; LifeScan). Blood glucose targets were: fasting, 4–7 mmol/l; postprandial, 5–9 mmol/l; 03:00, 4–7 mmol/l
Comparator	NPH (Insulatard 100 IU/ml; Novo Nordisk A/S, Gentofte, Denmark) 21:00 and 23:00 and HSI (Actrapid 100 IU/ml, Novo Nordisk A/S) 30 min before each main meal as subcutaneous injections. Insulin administration and blood glucose targets matched those for the detemir arm
Outcome measures	**Hypoglycaemia** Hypoglycaemia (all) Hypoglycaemia was defined as blood glucose < 3mmol/l with or without symptoms. Episodes were classified as minor if the subjects dealt with the episode themselves and as major if help froma third party or intravenous glucose or glucagon treatment was required. Major hypoglycaemia
Loss to follow up	0
Additional comments	No baseline characteristics reported for trial arms

Study arms

Detemir (N = 57) Once daily Insulin detemir with human insulin
NPH (N = 56) Once daily NPH insulin with human insulin

Characteristics

Study-level characteristics

	Study (N = 56)
% Female	
Sample Size	n = 10 ; % = 17.9
Mean age (SD)	
Mean/SD	34.5 (NR)
BMI (kg/m²)	
Mean/SD	23.8 (2)
Duration of diabetes (years)	
Mean/SD	14.8 (NR)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation process)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High (No information about a wash-out period between treatments)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns (No information about statistical tests for carry-over)
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information about randomisation process.No information about statistical tests for carry-over and no evidence of a wash-out period between treatments)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
	Overall Directness	Directly applicable

Home 2012

Home, 2012

Bibliographic Reference	Home, P D; Meneghini, L; Wendisch, U; Ratner, R E; Johansen, T; Christensen, T E; Jendle, J; Roberts, A P; Birkeland, K I; Improved health status with insulin degludec compared with insulin glargine in people with type 1 diabetes.; Diabetic medicine : a journal of the British Diabetic Association; 2012; vol. 29 (no. 6); 716-20

Study details

Study type	Randomised controlled trial (RCT) Follow-up article from Birkeland 2011, reporting quality of life outcomes
Study location	Australia, Germany, Norway, Sweden, USA
Study setting	28 centres across Australia, Germany, Norway, Sweden and the US
Study dates	Not specified
Duration of follow-up	16 weeks
Sample size	118 people Study presents data for Degludec (A) and Glargine arm from Birkeland 2011 study.
Inclusion criteria	Patients aged 18-75 years of age diagnosed with type 1 diabetes ≥12 months before study, treated continually with insulin using any regimen, and having an A1C of 7.0-11.0%.
Exclusion criteria	Pregnant or breast-feeding women People with clinically significant concomitant illnesses, impaired renal and hepatic function, and a history of recurrent major hypoglycemia or of hypoglycemia unawareness.
Intervention(s)	Degludec: Degludec (A) - Degludec U100- 600µmol/L - 1 unit = 6 nmol For further information, see Birkeland 2011
Comparator	Glargine U100/mL For further information, see Birkeland 2011
Outcome measures	**QoL** Measured using SF-36 version 2: Physical component Mental component
Loss to follow up	See Birkeland 2011
Methods of analysis	Participants' health status was measured at baseline and at 16 weeks using the SF-36 version 2. Changes in all eight domains of the SF-36 and physical and mental component scores were analysed by ANOVA, with treatment, country and sex as fixed effects, and age, baseline HbA1c and baseline values as covariates. The SF-36 does not have a fixed minimal important difference in diabetes. However, Cohen's effect size is noted in the SF-36 user manual as an oft-cited minimal important difference criterion An effect size of 0.2 is considered 'small', 0.5 'moderate' and 0.8 'large'

Additional comments	Study provides further data from Birkeland 2011 study.

Study arms

Glargine (N = 59) Glargine U100 Insulin glargine, combined with mealtime insulin aspart
Degludec (N = 59) Degludec U100 Insulin degludec, combined with mealtime insulin aspart

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Participants were aware of treatment arms. Study states that some participants has used glargine pre-study and changing to other insulin preparation sould have induced increased mental burden. Potential bias introduced for subjective outcomes.)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Open label trial. Potential bias introduced for subjective outcomes.)
	Overall Directness	Directly applicable

Home 2005

Home, 2005

Bibliographic Reference	Home, P D; Rosskamp, R; Forjanic-Klapproth, J; Dressler, A; European Insulin Glargine Study, Group; A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes.; Diabetes/metabolism research and reviews; 2005; vol. 21 (no. 6); 545-53

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	12 European countries
Study setting	63 centres
Study dates	Not reported
Duration of follow-up	28 weeks
Sources of funding	Aventis Pharma
Inclusion criteria	History of Type 1 diabetes and treated with insulin for at least 1 year Post-prandial serum C-peptide levels of <0.50 nmol/L or <1.50 µg/L when the capillary blood glucose level was ≥5.5 mmol/L (≥100 mg/dL)
Exclusion criteria	Not reported
Intervention(s)	Glargine U100 Once-daily dose of insulin glargine, given at bedtime, aiming for a target of 4.4–6.7 mmol/L (80–120 mg/dL) averaged over at least2–4 days with an absence of nocturnal hypoglycaemia. Given in combination with unmodified human insulin, injected before meals, aiming for a pre-meal blood glucose concentration of 4.4–6.7 mmol/L
Comparator	Once- (bedtime) or twice-daily NPH insulin, according to participant's prior treatment regimen. Blood glucose targets and bolus insulin was the same as those in the glargine arm

Outcome measures	**HbA1c** Change in HbA1c (%) **Hypoglycaemia** Hypoglycaemia was categorised as symptomatic (clinical symptoms confirmed by blood glucose <2.8mmol/L [<50mg/dL]) or asymptomatic (confirmed by blood glucose <2.8 mmol/L [<50 mg/dL] without symptoms). Hypoglycaemia (all) Major hypoglycaemia - Defined as requiring assistance from another person with either a blood glucose level <2.8 mmol/L [50 mg/dL] or prompt recovery after adminstration or oral carbohydrate, intravenous glucose or glucagon. Nocturnal hypoglycaemia Nocturnal hypoglycaemia was defined as occurring during sleep between bedtime and rising in the morning, or before the morning pre-breakfast self-blood glucose measurement and the morning insulin injection. **Adverse events** Adverse events- possibly related to study treatment Serious AEs- treatment emergent **Injection site reaction**
Loss to follow up	Withdrawals Glargine: 15 NPH: 21 The principal reason for withdrawal in both groups was that the person did not wish to continue (insulin glargine, n = 7; NPH insulin, n = 10).

Study arms

Glargine (N = 292) Glargine U100 Once-daily glargine with unmodified human insulin
NPH (N = 293) Once- or twice-daily NPH with unmodified human insulin

Characteristics

Arm-level characteristics

	Glargine (N = 292)	NPH (N = 293)
% Female		
Nominal	45.2	43.3
Age (years)		
Mean/SD	39 (12)	39 (12)
BMI (kg/m²)		
Mean/SD	24.6 (3.1)	25.1 (3.3)
HbA1c (%)		
Mean/SD	7.9 (1.2)	8 (1.2)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Some concerns for subjective outcomes such as adverse events.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low (Some concerns for subjective outcomes such as adverse events. Open label study design could have influenced subjective outcomes.)
	Overall Directness	Directly applicable

Home 2015

Home, 2015

Bibliographic Reference	Home, Philip D; Bergenstal, Richard M; Bolli, Geremia B; Ziemen, Monika; Rojeski, Maria; Espinasse, Melanie; Riddle, Matthew C; New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4).; Diabetes care; 2015; vol. 38 (no. 12); 2217-25

Study details

Study type	Randomised controlled trial (RCT)
Trial registration number	NCT01683266
Study location	Multinational (Canada, Czech Republic, Denmark, Estonia, Finland, Hungary, Japan, Latvia, Netherlands, Romania, Sweden and USA)
Study setting	Multicentre
Study dates	Not specified
Duration of follow-up	6 months
Sources of funding	Sanofi was the sponsor and coordinated the study, monitored clinical sites, collected and managed the data, and performed statistical analyses.
Inclusion criteria	≥18 years of age, type 1 diabetes for >1 year, and use of any mealtime insulin analog for ≥3 months.
Exclusion criteria	HbA1c <7.0 and>10.0% (<53 and>86 mmol/mol); ,1 year on a basal plus mealtime insulin regimen; insulin dose not stable (±20%) within 30 days; use of other mealtime, premix insulin, or other glucose-lowering medication within 3 months; and pump therapy within 6 months
Method of allocation	Randomisation conducted using a central treatment system (voice or web)
Intervention(s)	Glargine U300 Once daily subcutaneous injection of Gla-300 (using a modified TactiPen pen injector [Sanofi]: 1.5-unit dose increments). As a morning or evening injection. Morning injection time was between prebreakfast and prelunch (inclusive) and evening at the evening meal until bedtime. Basal insulin dose on day -1 was used to determine the starting dose, modulated by the median fasting SMPG of the last 3 days. Gla-300 titrated to a prebreakfast SMPG of 80–130 mg/dL (4.4–7.2 mmol/L). Dose adjustments of basal insulin were to be made weekly (no more than every 3–4 days). Mealtime insulin continued with a target range of 160 mg/dL (<8.9mmol/L) for 2-h postprandial plasma glucose, adjusted at investigator discretion.
Comparator	Glargine U100 Once daily subcutaneous injection of Gla-100 (SoloSTAR pen [Sanofi]: 1-unit dose increments) and as a morning or evening injection. Morning injection time was between prebreakfast and prelunch (inclusive) and evening at the evening meal until bedtime. Basal insulin dose on day -1 was used to determine the starting dose,modulated by the median fasting SMPG of the last 3 days. Gla-100 titrated to a prebreakfast SMPG of 80–130 mg/dL (4.4–7.2 mmol/L). Dose adjustments of basal insulin were to be made weekly (no more than every 3–4 days). Mealtime insulin continued with a target range of 160 mg/dL (<8.9mmol/L) for 2-h postprandial plasma glucose, adjusted at investigator discretion.

Outcome measures	**HbA1c** Change in HbA1c (%) % of participants achieving HbA1c <7.0% **Hypoglycaemia** Hypoglycaemia (all) - no. of patients experiencing one or more confirmed (≤ 70 mg/dL) or severe hypoglycaemic events Severe hypoglycaemia - no. of patients experiencing one or more events The predefined definition was confirmed or severe hypoglycaemia (all severe and all documented symptomatic and asymptomatic hypoglycaemia). Nocturnal hypoglycaemia Nocturnal hypoglycaemia was also predefined as of interest, and as episodes between midnight and 0559 h inclusive. **Adverse events** Adverse events- no. of participants with treatment-emergent AE Serious AEs **Injection site reaction** **Body weight** Change in body weight **QoL** Satisfaction - Diabetes Treatment Satisfaction Questionnaire (DTSQs) - change in score Quality of life- EuroQoL-5 (EQ-5D) - change in score
Loss to follow up	Glargine U300: 43 permanently discontinued- adverse event (3), lack of efficacy (4), poor compliance to protocol (9), other (26), missing (1) Glargine U100: 39 permanently discontinued- adverse event (4), lack of efficacy (1), poor compliance to protocol (4), other (30)

Study arms

Glargine U300 (N = 274) Once daily with mealtime insulin
Glargine U100 (N = 275) Once daily with mealtime insulin

Characteristics

Arm-level characteristics

	Glargine U300 (N = 274)	Glargine U100 (N = 275)
% Female		
Sample Size	n = 125 ; % = 45.6	n = 111 ; % = 40.4
Mean age (SD)		
Mean/SD	46.4 (13.9)	48.2 (13.4)
BMI		
Mean/SD	27.6 (5.5)	27.6 (4.7)
Body weight (kg)		
Mean/SD	81.9 (20.4)	81.8 (16.8)
HbA1c (%)		
Mean/SD	8.11 (0.77)	8.14 (0.79)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open label trial could have influenced subjective outcomes (adverse events, quality of life measures and satisfaction measures))
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns (Hypoglycaemia was also measured using HFSII questionnaire but data was not presented.)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Overall bias and Directness	Risk of bias judgement	Some concerns (Open label trial could have influenced subjective outcomes (adverse events, quality of life measures and satisfaction measures). Selective reporting of data (HFSII data not reported).)
	Overall Directness	Partially applicable (Study does not specify which bolus insulins were used by the participants.)

Home 2018a

Home, 2018

Bibliographic Reference	Home, Philip D; Bergenstal, Richard M; Bolli, Geremia B; Ziemen, Monika; Rojeski, Maria; Espinasse, Melanie; Riddle, Matthew C; Glycaemic control and hypoglycaemia during 12 months of randomized treatment with insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 1 diabetes (EDITION 4).; Diabetes, obesity & metabolism; 2018; vol. 20 (no. 1); 121-128

Study details

Study type	Randomised controlled trial (RCT) Extension of Home 2015
Trial registration number	NCT01683266
Study location	See Home 2015
Study setting	See Home 2015
Study dates	See Home 2015
Duration of follow-up	1 year (extension of Home 2015 trial)
Sources of funding	See Home 2015
Sample size	468
Inclusion criteria	See Home 2015
Exclusion criteria	See Home 2015
Method of allocation	See Home 2015
Intervention(s)	Glargine U300 See Home 2015 for further details.
Comparator	Glargine U100 See Home 2015 for further details.

Outcome measures	**HbA1c** Change in HbA1c (%) **Hypoglycaemia** Hypoglycaemia (all) -no of patients reporting ≥1 episodes of confirmed or severe hypoglycaemia (≤3.9 mmol/L (≤70 mg/dL)) Severe hypoglycaemia - no. of patients reporting at least 1 episode. “severe” hypoglycaemia was defined as an event that required assistance. Nocturnal hypoglycaemia Episode occurring between 00:00 and 05:59 **Adverse events** Adverse events Serious adverse event **Injection site reactions** **QoL** Change in EQ-5D single utility score Change in total DTSQs score Change in HFS-II score
Loss to follow up	Glargine U300 -12 permanently discontinued due to: adverse events (2), lack of efficacy (1), poor compliance (3), and other (6) Glargine U100 -11 permanently discontinued due to: adverse events (0), lack of efficacy (1), poor compliance (2), and other (8)

Study arms

Glargine U300 (N = 219) Once daily with meal time insulin (see Home 2015 for further details)
Glargine U100 (N = 225) Once daily with meal time insulin (see Home 2015 for further details)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open label trial could have infulenced subjective outcomes (adverse events, quality of life measures and satisfaction measures)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Open label trial could have influenced subjective outcomes (adverse events, quality of life measures and satisfaction measures).)
	Overall Directness	Partially applicable (Study does not specify which bolus insulins were used by the participants.)

Home 2018b

Home, 2018

Bibliographic Reference	Home, Philip D; Lam, Raymond L H; Carofano, Wendy L; Golm, Gregory T; Eldor, Roy; Crutchlow, Michael F; Marcos, Michael C; Rosenstock, Julio; Hollander, Priscilla A; Gallwitz, Baptist; Efficacy and safety of MK-1293 insulin glargine compared with originator insulin glargine (Lantus) in type 1 diabetes: A randomized, open-label clinical trial.; Diabetes, obesity & metabolism; 2018; vol. 20 (no. 9); 2220-2228

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	8 countries
Study setting	67 centres
Study dates	Not reported
Duration of follow-up	52 weeks
Sources of funding	Merck & Co. Inc.
Sample size	508
Inclusion criteria	Aged 18 years and above HbA1c ≤11.0% BMI <45.0 kg/m² History of Type 1 diabetes For 1 year or more Treated on a basal-bolus insulin regimen Intermediate or long-acting basal insulin at a total daily dose of ≥10 U/d together with a prandial insulin analog (insulins lispro, aspart, or glulisine)
Exclusion criteria	Recurrent major hypoglycaemia Allergy to insulin Signs of heart disease or heart failure
Intervention(s)	Glargine biosimilar (MK-1293, Merck & Co.) given once daily in the evening, justprior to bedtime, except for participants who were already taking Sanofi once daily at another time. Insulin was administered with an adapted version of the Haselmeier iPen platform pen injector, with initial dose based on participant's previous insulin use. Fasting plasma glucose target was: >70 mg/dL (>3.9 mmol/L) to ≤100 mg/dL (≤5.6 mmol/L)
Comparator	Glargine (Sanofi, Lantus) given once daily in the evening, justprior to bedtime, except for participants who were already taking Sanofi once daily at another time. Insulin was administered with the TactiPen pen injector, with initial dose based on participant's previous insulin use. Fasting plasma glucose target was: >70 mg/dL (>3.9 mmol/L) to ≤100 mg/dL (≤5.6 mmol/L)

Outcome measures	**HbA1c** Change in HbA1c (%) (24 weeks and 52 weeks) Participants achieving HbA1c <7% (24 weeks and 52 weeks) **Hypoglycaemia** Hypoglycaemia (all)- Defined as events were defined as instances of documented plasma glucose ≤70 mg/dL (≤3.9 mmol/L) and/or symptoms possibly due to hypoglycaemia. Severe hypoglycaemia - Defined as event for which participants required the assistance of another individual. Nocturnal hypoglycaemia Defined as events occurring between midnight and 0800. **Adverse events** Adverse events- no. of people with drug related AE Serious AEs **Injection site reactions** **Body weight** Change in body weight (kg)
Loss to follow up	MK- Gla : 20 Glargine U100: 12

Study arms

MK-1293 glargine biosimilar (N = 245) MK-1293 glargine biosimilar, given once per day in the evening, in combination with pre-trial bolus insulin
Glargine (N = 263) Insulin glargine (Lantus, Sanofi), given once per day in the evening, in combination with pre-trial bolus insulin

Characteristics

Arm-level characteristics

	MK-1293 glargine biosimilar (N = 245)	Glargine (N = 263)
Age (years)		
Mean/SD	41.8 (14.5)	41.6 (14.8)
% Female		

	MK-1293 glargine biosimilar (N = 245)	Glargine (N = 263)
Nominal	43.3	42.2
BMI (kg/m²)		
Mean/SD	26.4 (4.4)	26.4 (4.7)
HbA1c (%)		
Mean/SD	8 (1.2)	8 (1.3)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation and allocation concealment)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information about randomisation and allocation concealment)
	Overall Directness	Partially applicable (Participants received different prandial insulins. Participants were to continue with their prandial insulin regimen (insulins lisrpo, aspart, or glulisine))

Home 2004

Home, 2004

Bibliographic Reference	Home, Philip; Bartley, Paul; Russell-Jones, David; Hanaire-Broutin, Helene; Heeg, Jan-Evert; Abrams, Pascale; Landin-Olsson, Mona; Hylleberg, Birgitte; Lang, Hanne; Draeger, Eberhard; Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group; Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial.; Diabetes care; 2004; vol. 27 (no. 5); 1081-7

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Australasia and Europe
Study setting	52 trial sites
Study dates	16 weeks (dates not reported)
Duration of follow-up	16 weeks
Sources of funding	Novo Nordisk
Sample size	409
Inclusion criteria	Aged 18 years and above BMI <35.5 kg/m² History of Type 1 diabetes For over 1 year Treated on a basal-bolus insulin regimen For over 2 months with basal insulin dose <100 units/day HbA1c <12.0%
Exclusion criteria	Proliferative retinopathy or maculopathy Recurrent major hypoglycaemia Pregnant or breast-feeding women Impaired hepatic or renal function Severe cardiac problems
Intervention(s)	Twice-daily treatment with insulin detemir (100 units/ml; Novo Nordisk, Bagsværd, Denmark). The insulin detemir group was further randomized into two groups: before breakfast and at bedtime, or at 12-h intervals. Mealtime insulin was supplied by the rapid-acting insulin analog insulin aspart (NovoRapid/NovoLog; Novo Nordisk). All insulin preparations were administered as subcutaneous injections using a NovoPen 3.0 device. Basal insulin doses were titrated to optimal levels over the first 4 weeks, or longer if necessary, based on self-monitored plasma glucose levels and the targets for blood glucose control (prebreakfast/night 4.0– 7.0 mmol/l; postprandial ≤10.0 mmol/l)
Comparator	Twice-daily treatment with NPH insulin (Novo Nordisk). NPH insulin was administered before breakfast and at bedtime. Mealtime insulin requirements were supplied by the rapid-acting insulin analog insulin aspart (NovoRapid/NovoLog; Novo Nordisk). Method of delivery and plasma glucose targets were the same as those used in the detemir arms

Outcome measures	**HbA1c** Change in HbA1c (%) **Hypoglycaemia** Hypoglycaemic episodes were classified as major (requiring assistance from another person), minor (glucose measurement < 2.8 mmol/l, with or without symptoms) Hypoglycaemia (all) Major hypoglycaemia Nocturnal hypoglycaemia Nocturnal hypoglycaemic was taken as an episode between 2300 and 0600 **Body weight** Change in weight (kg)
Loss to follow up	17
Additional comments	Study randomised patients to two different twice daily detemir regimens: before breakfast and at bedtime or at 12 hour interval. Data was extracted for the following arms: Detemir - before breakfast and at bedtime NPH - before breakfast and at bedtime

Study arms

Detemir (every 12 hours) (N = 137) Insulin detemir with rapid-acting insulin aspart. Detemir given twice-daily (at 12 hour intervals) Data was not extracted for this arm.
Detemir (morning and bedtime) (N = 139) Insulin detemir with rapid-acting insulin aspart. Detemir given twice-daily (before breakfast and at bedtime)
NPH (N = 132) NPH insulin with rapid-acting insulin aspart. NPH given twice-daily (before breakfast and at bedtime)

Characteristics

Arm-level characteristics

	Detemir (every 12 hours) (N = 137)	Detemir (morning and bedtime) (N = 139)	NPH (N = 132)
% Female			
Nominal	48	43	47
Age (years)			
Mean/SD	40.9 (13)	41.3 (11.4)	38.3 (12.4)
BMI (kg/m²)			
Mean/SD	25.1 (3.3)	25.2 (3.6)	25.2 (3.7)
HbA1c			
Mean/SD	8.55 (1.2)	8.74 (1.2)	8.52 (1.19)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation and allocation concealment)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open label trial may have had an impact on self-reported outcomes such as hypoglycaemia.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information about randomisation and allocation concealment. Open label trial may have had an impact on self-reported outcomes such as hypoglycaemia (as this included symptomatic only))
	Overall Directness	Directly applicable

Iga 2017

Iga, 2017

Bibliographic Reference	Iga, R.; Uchino, H.; Kanazawa, K.; Usui, S.; Miyagi, M.; Kumashiro, N.; Yoshino, H.; Ando, Y.; Hirose, T.; Glycemic Variability in Type 1 Diabetes Compared with Degludec and Glargine on the Morning Injection: An Open-label Randomized Controlled Trial; Diabetes Therapy; 2017; vol. 8 (no. 4); 783-792

Study details

Study type	**Crossover randomised controlled trial**
Study location	Japan
Study setting	Toho University School of Medicine
Study dates	Not reported
Duration of follow-up	12 weeks
Sources of funding	None
Sample size	20
Inclusion criteria	History of Type 1 diabetes For at least 1 year Aged 20 years and older
Exclusion criteria	Proliferative retinopathy or maculopathy Pregnant or breast-feeding women History or presence of cancer History of cardiovascular disease or stroke, or blood pressure beyond the normal range Active infectious diseases
Method of allocation	The study included 20 participants who were randomised by computer-generated assignment to receive first either degludec or glargine continuously for 12 weeks.
Intervention(s)	Degludec (concentration unknown) Insulin degludec for 12 weeks (period 1), followed by 12 weeks of insulin glargine. Both were given once daily in the morning, and in combination with mealtime aspart. Target fasting blood glucose levels were 80–110 mg/dL (4.5–6.1 mmol/L). Target postprandial blood glucose levels were 80–140 mg/dL (4.5–7.8 mmol/L)
Comparator	Glargine (concentration unknown)

Study type	Crossover randomised controlled trial
	Insulin glargine for 12 weeks (period 1), followed by 12 weeks of insulin degludec. Both were given once daily in the morning, and in combination with mealtime aspart.
Outcome measures	**HbA1c** HbA1c (%) at follow up **Nocturnal hypoglycaemia** **% time spent in nocturnal hypoglycaemia** **% time spent in hypoglycaemia** **% time spent in target glucose range** 70 and 140 mg/dL (3.9–7.8 mmol/L)

Study arms

Degludec (N = 10) Concentration unknown Once daily Insulin degludec (period 1), followed by glargine (period 2). In both periods, insulin was given once daily, every morning, in combination with mealtime insulin aspart
Glargine (N = 10) Concentration unknown Once daily Insulin glargine (period 1), followed by degludec (period 2). In both periods, insulin was given once daily, every morning, in combination with mealtime insulin aspart

Characteristics

Arm-level characteristics

	Degludec (N = 10)	Glargine (N = 10)
% Female		
Sample Size	n = 5 ; % = 50	n = 4 ; % = 40
Age (years)		
Mean/SD	55 (14)	53 (18)
BMI (kg/m²)		
Mean/SD	24.4 (4.4)	23.1 (4.1)
HbA1c (%)		

	Degludec (N = 10)	Glargine (N = 10)
Mean/SD	7.1 (0.9)	7.7 (0.6)
Duration of diabetes (years)		
Mean/SD	14.4 (8.6)	16.1 (8.7)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Some concerns (No washout period but outcomes only assessed in final week of treatment)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns (No information about a statistical test for carry-over)
Overall bias and Directness	Risk of bias judgement	Some concerns (No washout period and no information about a statistical test for carry-over)
	Overall Directness	Partially applicable (Concentration of glargine and degludec not specified.)

Iwamoto 2013

Iwamoto, 2013

Bibliographic Reference	Iwamoto, Y.; Clauson, P.; Nishida, T.; Kaku, K.; Insulin degludec in Japanese patients with type 1 diabetes mellitus: A randomized controlled trial; Journal of Diabetes Investigation; 2013; vol. 4 (no. 1); 62-68

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Japan
Study setting	8 centres
Study dates	January - May 2009
Duration of follow-up	6 weeks
Sources of funding	Novo Nordisk
Sample size	65
Inclusion criteria	BMI <30.0 kg/m² History of Type 1 diabetes For at least 12 months Treated on a basal-bolus insulin regimen For at least 12 months, with either glargine or NPH as the basal insulin and aspart as the bolus component HbA1c <10.4% Aged 20 years and older
Exclusion criteria	Recurrent major hypoglycaemia Pregnant or breast-feeding women Impaired hepatic or renal function Hypoglycaemic unawareness
Intervention(s)	Insulin degludec, administered once-daily at bedtime, using the same starting dose as pretrial basal insulin. Insulin aspart was administered three times per day at mealtimes, using the same dose as the pretrial period. All insulin was injected subcutaneously using NovoPen® 300 (Novo Nordisk A/S, Bagsværd, Denmark) for insulin degludec and FlexPen® (Novo Nordisk A/S) for insulin aspart. Fasting plasma glucose target was 80–109 mg/dL g/dL. Bolus insulin doses were adjusted at the investigator's discretion.
Comparator	Insulin detemir, administered once-daily at bedtime, using the same starting dose as pretrial basal insulin. Insulin aspart was administered three times per day at mealtimes, using the same dose as the pretrial period. All insulin was injected subcutaneously using FlexPen® (Novo Nordisk A/S). Fasting plasma glucose targets were the same as in the degludec arm

Outcome measures	**Hypoglycaemia** Hypoglycaemia (all) Serious hypoglycaemia - Hypoglycaemia categorized as severe (requiring the assistance of another person), confirmed (associated with a measured plasma glucose ≤55 mg/dL) and symptoms-only (symptomatic with measured plasma glucose ≥56 mg/dL or without plasma glucose measurement). Nocturnal hypoglycaemia Nocturnal hypoglycaemia was defined as an event occurring after 23.00 hours and before 06.00 hours. **Adverse events** Adverse events

Study arms

Degludec (N = 33) Once-daily insulin degludec with mealtime insulin aspart
Detemir (N = 32) Once-daily insulin detemir with mealtime insulin aspart

Characteristics

Arm-level characteristics

	Degludec (N = 33)	**Detemir (N = 32)**
% Female		
Nominal	27.3	40.6
Age (years)		
Mean/SD	45.5 (15)	43.2 (15.4)
BMI (kg/m²)		
Mean/SD	22.92 (2.49)	22.87 (2.5)
HbA1c (%)		
Mean/SD	7.79 (0.86)	7.72 (0.86)
Cochrane Risk of Bias Tool 2.0		

	Degludec (N = 33)	Detemir (N = 32)
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

Jinnouchi 2015

Jinnouchi, 2015

Bibliographic Reference	Jinnouchi, H.; Koyama, M.; Amano, A.; Takahashi, Y.; Yoshida, A.; Hieshima, K.; Sugiyama, S.; Kurinami, N.; Jinnouchi, T.; Becker, R.; Continuous Glucose Monitoring During Basal-Bolus Therapy Using Insulin Glargine 300 U mL-1 and Glargine 100 U mL-1 in Japanese People with Type 1 Diabetes Mellitus: A Crossover Pilot Study; Diabetes Therapy; 2015; vol. 6 (no. 2); 143-152

Study details

Study type	Crossover randomised controlled trial
Study location	Japan
Study setting	Hospital setting
Study dates	Not specified
Duration of follow-up	8.4 weeks
Sources of funding	Stdy sponsored by Sanofi.
Sample size	20

Study type	Crossover randomised controlled trial
Inclusion criteria	Japanese people of at least 20 years of age with T1DM who were being treated with basal–bolus insulin and had glycated haemoglobin (HbA1c) within the range 6.5–10.0%, and a median fasting self-monitored plasma glucose (SMPG) concentration of ≤13 mmol L-1 (240 mg dL-1) in the 3 days prior to randomization
Exclusion criteria	People who received premix insulin or basal insulin other than Gla-100, neutral protamine Hagedorn insulin, neutral protamine insulin lispro, or insulin detemir, or mealtime insulin other than insulin lispro, aspart, or glulisine during the 4 weeks immediately before screening.
Intervention(s)	Glargine U300 Participants received either Gla-300 (using a modified TactiPen; Haselmeier GmbH,Zurich, Switzerland) in treatment period 1 followed by Gla-100 (using a SoloSTAR pen; Sanofi, Paris, France) in treatment period 2 (subgroup 1). Study insulin preparations were self-administered subcutaneously once daily at bedtime (preferably [3 h after evening mealtime insulin). The starting dose for both treatment periods was based on the basal insulin dose in the screening period. Owing to differences in the scaling of the two injection devices, starting doses of Gla-300 were divisible by 1.5 U and did not exceed the previous daily dose. Basal insulin dose was titrated to achieve fasting SMPG in the range 4.4–7.2 mmol L-1 (80–130 mg dL-1) during the two treatment periods. The mealtime insulin dose was to continue without adjustment from the participant's pre-study regimen as much as possible, with adjustment allowed at the discretion of the investigator or participant if postprandial hyperglycaemia (2-h postprandial plasma glucose >8.9 mmol L-1[>160 mg dL-1]) or an abnormality relevant to hypoglycaemia caused by mealtime insulin was observed and it was difficult to avoid the occurrence of abnormalities by adjusting the basal insulin dose.
Comparator	Glargine U100 Participants received either Gla-100 (using a SoloSTAR pen; Sanofi, Paris, France) in treatment period 1 followed by Gla-300 (using a modified TactiPen; Haselmeier GmbH,Zurich, Switzerland) in treatment period 2. Study insulin preparations were self-administered subcutaneously once daily at bedtime (preferably [3 h after evening mealtime insulin). The starting dose for both treatment periods was based on the basal insulin dose in the screening period. Gla-100 starting doses were equal to the previous daily dose. Basal insulin dose was titrated to achieve fasting SMPG in the range 4.4–7.2 mmol L-1 (80–130 mg dL-1) during the two treatment periods. The mealtime insulin dose was to continue without adjustment from the participant's pre-study regimen as much as possible, with adjustment allowed at the discretion of the investigator or participant if postprandial hyperglycaemia (2-h postprandial plasma glucose >8.9 mmol L-1[>160 mg dL-1]) or an abnormality relevant to hypoglycaemia caused by mealtime insulin was observed and it was difficult to avoid the occurrence of abnormalities by adjusting the basal insulin dose.
Outcome measures	**Hypoglycaemia** Hypoglycaemia (all)- Defined as confirmed (≤3.9 mmol L-1 [≤70 mg dL-1]) or severe hypoglycaemia

Study type	Crossover randomised controlled trial
	Nocturnal hypoglycaemia confirmed (≤ 3.9 mmol L-1 or severe hypoglycaemia) Nocturnal hypoglycaemia defined as occurring between 00:00 and 05:59. **Adverse events** Adverse events - treatment emergent AEs
Loss to follow up	0

Study arms

Glargine U300 (N = 10) Glargine U300 once daily (period 1) Glargine U100 once daily (period 2) With meal time insulin
Glargine U100 (N = 10) Glargine U100 once daily (period 1) Glargine U300 once daily (period 2) With meal time insulin

Characteristics

Arm-level characteristics

	Glargine U300 (N = 10)	Glargine U100 (N = 10)
% Female		
No of events	n = 6 ; % = 60	n = 6 ; % = 60
Mean age (SD)		
Mean/SD	52.1 (17.3)	52.1 (15.3)
BMI		
Mean/SD	24.1 (4.4)	22.6 (1.9)
Body weight (kg)		
Mean/SD	61.5 (13.2)	57 (8)
HbA1c (%)		

	Glargine U300 (N = 10)	Glargine U100 (N = 10)
Mean/SD	8.49 (0.87)	7.93 (0.7)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information on allocation concealment and randomisation.)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Some concerns (No information on washout period.)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns (Open label trial could have influenced subjective outcomes such as adverse events)
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No information on allocation concealment and randomisation. No information on washout period. Open label trial could have influenced subjective outcomes such as adverse events)
	Overall Directness	Partially applicable *(Study does not specify which bolus insulins were used by the participants.)*

Karanova 2020

Karonova, 2020

Bibliographic Reference	Karonova, T.L.; Mosikian, A.A.; Mayorov, A.Y.; Makarenko, I.E.; Zyangirova, S.T.; Afonkina, O.A.; Belikova, T.M.; Zalevskaya, A.G.; Khokhlov, A.L.; Drai, R.V.; Safety and efficacy of GP40061 compared with originator insulin glargine (Lantus): A randomized open-label clinical trial; Journal of Comparative Effectiveness Research; 2020; vol. 9 (no. 4); 263-273

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Russia
Study setting	14 centres
Study dates	Not reported
Duration of follow-up	26 weeks
Sources of funding	OOO GEROPHARM, Russia
Sample size	180
Inclusion criteria	Aged 18 years and above 18-65 BMI 18.5 - 30.0 kg/m² History of Type 1 diabetes For at least 12 months Treated on a basal-bolus insulin regimen For at least 30 days HbA1c 6.5% - 12.0%
Exclusion criteria	Recurrent major hypoglycaemia Allergy to insulin advanced stages of several DM complications (proliferative diabetic retinopathy, severe peripheral diabetic neuropathy or autonomic neuropathy, diabetic nephropathy with estimated glomerular filtration rate (eGFR) <45 ml/min/1.73-m2, diabetic foot syndrome)
Intervention(s)	Insulin glargine biosimilar (GP40061), delivered through pre-filled pen injectors. The initial dose of insulin was determined based on previous insulin therapy. Participants were not allowed to change the type of bolus insulin they used at baseline
Comparator	Insulin glargine (Sanofi Lantus), delivered through pre-filled pen injectors. The initial dose of insulin was determined based on previous insulin therapy. Participants were not allowed to change the type of bolus insulin they used at baseline

Outcome measures	**HbA1c** Change in HbA1c (%) Participants achieving glycaemic goal **Hypoglycaemia** Severe hypoglycaemia- Definition not provided. Nocturnal hypoglycaemia Definition not provided. **Adverse events** Adverse events - related to study drug Serious AEs **Injection site reaction** **Body weight** Change in weight (kg) **QoL** Change in DTSQ total score
Loss to follow up	GP-Gla : Early withdrawal (2), participants decision (1), lost to follow up (1) Glargine U100 : Early withdrawal (1), participants decision (1),

Study arms

GP-Gla (Glargine biosimilar) (N = 90) GEROPHARM GP-Gla (GP40061) once daily in combination with bolus insulin (same bolus insulin as at baseline)
Sa-Gla (N = 90) Sanofi glargine (Lantus) once daily in combination with bolus insulin (same bolus insulin as at baseline)

Characteristics

Arm-level characteristics

	GP-Gla (Glargine biosimilar) (N = 90)	Sa-Gla (N = 90)
% Female		
Nominal	46.7	47.8

	GP-Gla (Glargine biosimilar) (N = 90)	Sa-Gla (N = 90)
BMI (kg/m²)		
Mean/SD	24.33 (3.11)	24.29 (3.16)
HbA1c (%)		
Mean/SD	8.62 (1.27)	8.68 (1.16)
Duration of diabetes		
Mean/SD	14.44 (9.85)	13.8 (10.25)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation and allocation concealement)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Limited information about analysis methods)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open label trial.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information about randomization or analysis methods. High - treatment satisfaction, hypoglycemia and adverse events- Open label trial could have influenced subjective outcomes.)
	Overall Directness	Partially applicable (Unclear which bolus insulins were given to participants)

Kolendorf 2006

Kolendorf, 2006

Bibliographic Reference	Kolendorf, K; Ross, G P; Pavlic-Renar, I; Perriello, G; Philotheou, A; Jendle, J; Gall, M-A; Heller, S R; Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes.; Diabetic medicine : a journal of the British Diabetic Association; 2006; vol. 23 (no. 7); 729-35

Study details

Study type	Randomised controlled trial (RCT) Cross-over trial
Study location	Australia, Europe and South Africa
Study setting	11 sites
Study dates	Not reported
Duration of follow-up	16 weeks (6 weeks titration, 10 weeks maintenance phase)
Sources of funding	Novo Nordisk
Sample size	131
Inclusion criteria	Aged 18 years and above BMI ≤35 kg/m² History of Type 1 diabetes For at least 1 year Treated on a basal-bolus insulin regimen For ≥4 months, with basal insulin (1, 2 or 3 times daily) in combination with mealtime aspart or lispro 3-4 times daily HbA1c ≤9% Total daily insulin dose ≤ 1.4 IU/kg per day and a basal insulin requirement ≥ 30% of the total daily insulin dose
Exclusion criteria	Recurrent major hypoglycaemia Allergy to insulin Pregnant or breast-feeding women Hypoglycaemic unawareness
Method of allocation	After a 2 week screening period, people were randomsied (1:1) to two 16-week treatment periods: one with detemir plus mealtime IAsp and one with NPH plus mealtime IAsp. The first 6 weeks of each treatment period were regarded as a titration phase, while the last 10 weeks were regaded as the maintenance phase.
Intervention(s)	Detemir (Levemir®; NovoNordisk A/S; 100 U/ml) before breakfast and bedtime and IAsp (NovoRapid ®, NovoNordisk A/S; 100 U/ml) immediately before each main meal as subcutaneous injections (basal insulin in the thigh and IAsp in the abdomen). Plasma glucose targets: 5–6 mmol/ l before breakfast, ≤6.0 mmol/ l before the evening meal, ≤ 8.0 mmol/l postprandially, i.e. 90 min after meals, and 6–8 mmol/l before bedtime
Comparator	NPH (NovoNordisk A/S, Bagsvaerd, Denmark; 100 IU/ml) before breakfast and bedtime and IAsp (NovoRapid ®, NovoNordisk A/S; 100 U/ml). Timing and method of delivery, and plasma glucose targets were the same as those for the detemir arm

Outcome measures	**HbA1c** Change in HbA1c (%)- calculated **Hypoglycaemia** Hypoglycaemic episodes were classified as severe if help from other was required, as confirmed if plasma glucose was <3.1 mmol/l and the individuals dealt with the episode themselves, and as symptomatic if episodes were not confirmed by a plasma measurement and no assistance was required. Hypoglycaemia (all) Severe hypoglycaemia - Defined as requiring help from others Nocturnal hypoglycaemia Defined as occurring between 23:00 to 06:00

Study arms

Detemir (N = 66) Twice daily (before breakfast and at bedtime) Period 1. Insulin detemir with mealtime insulin aspart; Period 2. NPH with mealtime insulin aspart
NPH (N = 64) Period 1. NPH insulin with mealtime insulin aspart; Period 2: Insulin detemir with mealtime insulin aspart

Characteristics

Arm-level characteristics

	Detemir (N = 66)	NPH (N = 64)
% Female		
Nominal	48.5	43.8
Age (years)		
Mean/SD	38.5 (12.3)	39.9 (12.4)
HbA1c (%)		
Mean/SD	7.9 (0.7)	7.9 (0.8)
Basal insulin dose (IU/kg)		
Mean/SD	0.35 (0.12)	0.36 (0.12)

	Detemir (N = 66)	NPH (N = 64)
Meal-time insulin dose (U/kg)		
Mean/SD	0.41 (0.13)	0.38 (0.13)

Cochrane Risk of Bias Tool 2.0		
Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation and allocation concealment)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No information on allocation concealment and randomisation. No information on statistical test for carryover.)
	Overall Directness	Directly applicable

Lane 2017

Lane, 2017

Bibliographic Reference	Lane, Wendy; Bailey, Timothy S; Gerety, Gregg; Gumprecht, Janusz; Philis-Tsimikas, Athena; Hansen, Charlotte Thim; Nielsen, Thor S S; Warren, Mark; Group, Information; SWITCH, 1; Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial.; JAMA; 2017; vol. 318 (no. 1); 33-44

Study details

Study type	Crossover randomised controlled trial
Study location	USA and Poland
Study setting	90 sites (84 USA, 6 Poland)
Study dates	January 2014 - January 2016
Duration of follow-up	32 weeks
Sources of funding	Novo Nordisk
Sample size	501
Inclusion criteria	Aged 18 years and above BMI ≤45 kg/m² History of Type 1 diabetes For a year or more Treated on a basal-bolus insulin regimen Treated with either a basal-bolus regimen or continuous subcutaneous insulin infusion for 26 weeks or more HbA1c ≤10% Fulfilled at least 1 of the pretrial risk criteria for developing hypoglycemia: (1) experienced 1 or more severe hypoglycemic episodes within the last year (based on ADA definition); (2) had moderate chronic renal failure (estimated glomerular filtration rate 30-59 mL/min/1.73 m2); (3) were unaware of their hypoglycemic symptoms; (4) had diabetes for more than 15 years; or (5) had an episode of hypoglycemia (symptoms, blood glucose level of ≤70 mg/dL, or both) within the last 12 weeks
Exclusion criteria	Received insulin degludec or insulin glargine U100 within the last 26 weeks before screening
Method of allocation	Patients were randomised 1:1 with a block size of 8 using a trial-specific central interactive voice or web-re3sponse system that used a simple sequential allocation randomisation schedule without stratifying factors, which could be accessed at nay time by authorised persons. Paitents were randomised 1:1 in a blinded manner. The trial was double blinded- all involved parties were blinded to insulin treatment allocation throughout the trial.
Intervention(s)	Degludec U100 Insulin degludec followed by insulin glargine U100. To eliminate confounding, within each treatment sequence patients were randomized 1:1 to administer basal insulin in either the morning (from waking up to breakfast) or the evening (from main evening meal to bedtime). Insulin aspart 100 U/mL was administered using a prefilled pen (FlexPen; Novo Nordisk). Insulin was administered subcutaneously, aiming for a fasting target of between 71 and 90mg/dL. Preprandial blood glucose target was between 71 and 108 mg/dL

Comparator	Glargine U100 Insulin glargine followed by insulin degludec. Methods of administration, timing and blood glucose targets were the same as those used for the degludec then glargine arm
Outcome measures	**Hypoglycaemia** Hypoglycaemia (all) - American Diabetes Assoication (ADA) definition used Severe hypoglycaemia - Defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions, neurological recovery following the return of plasma glucose to normal, or both Nocturnal hypoglycaemia Defined as occurring between 12:01am and 5:59am. **Adverse events** Adverse events -probably related to trial product Serious AEs - probably related to trial product **Body weight** Change in weight (kg)
Loss to follow up	One patient withdrew before treatment exposure. Overall, 395 (78.8%) patients completed the trial. The proportion of patients and the reasons for withdrawing from the trial were similar between treatments (insulin degludec, 11.0%; insulin glargine U100, 12.2%). The most common reasons for withdrawal in both treatment groups were withdrawal by patient and adverse events. Patients discontinuing before the first maintenance period were similar to those with observation time during the first maintenance period.
Methods of analysis	Change from baseline in HbA1c after 32 weeks of treatment was analysed separately for each treatment period, with a mixed model for repeated measurements including treatment, visit, sex, region, pretrial insulin regimen, and dosing time as fixed effects, and age and baseline HbA1c, as cocariates.

Study arms

Degludec (N = 249)
Degludec U100 Insulin degludec with mealtime aspart (period 1) followed by glargine with mealtime aspart (period 2)
Glargine (N = 252)
Glargine U100 Insulin glargine with mealtime aspart (period 1) followed by degludec with mealtime aspart (period 2)

Characteristics

Arm-level characteristics

	Degludec (N = 249)	Glargine (N = 252)
% Female		
Nominal	49.4	43.3
Age (years)		
Mean/SD	45.4 (13.7)	46.4 (14.6)
BMI (kg/m²)		
Mean/SD	27.9 (5.1)	27 (4.5)
HbA1c (%)		
Mean/SD	7.7 (1)	7.5 (1)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

Le Floch 2009

Le Floch, 2009

Bibliographic Reference	Le Floch, Jean-Pierre; Levy, Marc; Mosnier-Pudar, Helen; Nobels, Frank; Laroche, Sylvie; Gonbert, Sophie; Eschwege, Eveline; Fontaine, Pierre; Assessment of Detemir Administration in Progressive Treat-to-Target Trial (ADAPT) Study, Group; Comparison of once- versus twice-daily administration of insulin detemir, used with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treat-to-target trial (ADAPT).; Diabetes care; 2009; vol. 32 (no. 1); 32-7

Study details

Study type	Randomised controlled trial (RCT)
Trial registration number	NCT00117780
Study location	France and Belgium
Study setting	Centers in France (193) and Belgium (6)
Study dates	Not provided. Study was received for publication in 2008.
Duration of follow-up	4 months
Sources of funding	Novo Nordisk
Sample size	512
Inclusion criteria	History of Type 1 diabetes For at least 1 year HbA1c 7.5-10%
Exclusion criteria	Other significant medical disorders Conditions capable of altering glucose control Hypoglycaemic unawareness Pregnancy Use of oral antidiabetes drugs Severe degenerative complications or associated disease And associated drugs
Method of allocation	The randomisation list was generated by computer using an aleatory function before the start of the trial and the Interactive Voice Response telephone randomisation system.
Intervention(s)	Once daily (at bedtime) injections of detemir, with bolus doses of insulin aspart (aspart) given three times daily at mealtimes. Insulins were supplied in 100 units/ml 3-ml FlexPen devices. After 1 month of intensive titration, patients were followed up over 3 more months, with primary end points being evaluated at the end of this period.
Comparator	Twice-daily (before breakfast and at bedtime) injections of detemir, with bolus doses of insulin aspart (aspart) given three times daily at mealtimes. Insulins were supplied in 100 units/ml 3-ml FlexPen devices. After 1 month of intensive titration, patients were followed up over 3 more months, with primary end points being evaluated at the end of this period.

Outcome measures	**HbA1c** Change in HbA1c (%) Participants achieving HbA1c < 7% **Hypoglycaemia** Frequency of hypoglycaemia (events per patient per 14 days)
Loss to follow up	Major protocol deviations were observed in 29 and 26 patients taking once-daily detemir (12%) and twice-daily detemir (10%), respectively. The most common deviations were no respect for randomisation (16 patients; 3.1%), delayed baseline A1C assay (14 patients; 2.7%), and A1C outside the nclusion range (4 patients; 0.8%). Five patients (1.0%) randomly assigned to once-daily detemir switched without consultation to twice-daily detemir. Twenty-three patients withdrew from the trial because of poor glycemic control (10 vs. 5 taking once-daily vs. twice-daily detemir, respectively, or discomfort (2 taking once-daily vs. 6 taking twice-daily detemir, respectively. All patients with major protocoldeviations were excluded from the per protocol population.

Study arms

Detemir once daily (N = 250) Detemir once daily (at bedtime) with insulin aspart given three times daily at mealtimes.
Detemir twice daily (N = 262) Detemir once daily (before breakfast and at bedtime) with insulin aspart given three times daily at mealtimes.

Characteristics

Study-level characteristics

	Study (N = 512)
% Female	
Sample Size	n = 243 ; % = 47
Mean age (SD)	
Mean/SD	41.5 (13)
BMI	
Mean/SD	25 (4)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

Mathieu 2013

Mathieu, 2013

Bibliographic Reference	Mathieu, Chantal; Hollander, Priscilla; Miranda-Palma, Bresta; Cooper, John; Franek, Edward; Russell-Jones, David; Larsen, Jens; Tamer, Soren Can; Bain, Stephen C; NN1250-3770 (BEGIN: Flex T1) Trial, Investigators; Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension.; The Journal of clinical endocrinology and metabolism; 2013; vol. 98 (no. 3); 1154-62

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Europe and USA
Study dates	Not reported
Duration of follow-up	26 weeks
Sources of funding	Novo Nordisk
Sample size	493
Inclusion criteria	Aged 18 years and above BMI <35.0 kg/m² Treated on a basal-bolus insulin regimen HbA1c ≤10%
Exclusion criteria	Not reported
Method of allocation	Eligible participants were randomised 1:1:1, using a central interactive voice/web response system. Trial product masking was maintained for titration surveillance monitors and statistical and medical personnel unit data were locked for analyses.
Intervention(s)	Degludec (100 U/mL, 3 mL FlexPen; Novo Nordisk, Bagsvaerd, Denmark) as either a Forced-Flex regimen (administered on Monday, Wednesday, and Friday mornings and on Tuesday, Thursday, Saturday, and Sunday evenings; ie, at fixed intervals with a minimum of 8 and a maximum of 40 hours between injections) or at the same time daily (once daily with evening meal). Both given in combination with mealtime aspart (NovoRapid/NovoLog, 100 U/mL, 3mLFlexPen; NovoNordisk). Doses were titrated to achieve a prebreakfast plasma glucose target of 4.0 –5.0 mmol/L. Bolus doses were titrated to a mean premeal plasma glucose target of less than 5.0 mmol/L
Comparator	Glargine (Lantus, 100 U/mL, 3 mL SoloStar; Sanofi, Paris, France) in combination with mealtime aspart NovoRapid/NovoLog, 100 U/mL, 3mLFlexPen;NovoNordisk). Plasma glucose targets matched those in the degludec arms

Outcome measures	**HbA1c** Change in HbA1c (%) **Hypoglycaemia** Hypoglycaemia (all) Severe hypoglycaemia Defined as blood glucose measurements of less than 3.1 mmol/L or severe episodes requiring assistance. Nocturnal hypoglycaemia Occurring between 0001 and 0559 hours. **Adverse events** Adverse events - AEs possibly/ probably related to basal insulin Serious AEs **Injection-site reactions** **Body weight** Change in weight
Loss to follow up	The percentage of participants withdrawn during the main trial from the IDeg Forced-Flex (15.9%), IDeg (15.8%) and IGlar group (7.3%).

Study arms

Degludec (forced-flex regimen) (N = 164) Degludec administered on Monday, Wednesday, and Friday mornings and on Tuesday, Thursday, Saturday, and Sunday evenings with mealtime Aspart. Data from this arm was not used.
Degludec (N = 165) Degludec U100 Degludec administered once per day with the evening meal and mealtime Aspart
Glargine (N = 164) Glargine U100 Glargine administered once per day, at the same time every day, and mealtime Aspart

Characteristics

Arm-level characteristics

	Degludec (forced-flex regimen) (N = 164)	Degludec (N = 165)	Glargine (N = 164)
% Female			
Nominal	37.8	43	46.3
Age (years)			
Mean/SD	42.6 (13.4)	44.5 (13.1)	44.1 (12.6)
HbA1c (%)			
Mean/SD	7.7 (1)	7.7 (0.9)	7.7 (0.9)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Open-label trial)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Open-label trial but objective outcomes)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low (Open-label trial but objective outcomes)
	Overall Directness	Directly applicable

Matsuhisa 2016a

Matsuhisa, 2016

Bibliographic Reference	Matsuhisa, M; Koyama, M; Cheng, X; Takahashi, Y; Riddle, M C; Bolli, G B; Hirose, T; EDITION JP 1 study, group; New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1).; Diabetes, obesity & metabolism; 2016; vol. 18 (no. 4); 375-83

Study details

Study type	Randomised controlled trial (RCT)
Trial registration number	NCT01689129
Study location	Japan
Study setting	22 centres in Japan
Study dates	October 2012 and October 2013
Duration of follow-up	6 months
Sources of funding	Study was funded by Sanofi
Sample size	243
Inclusion criteria	Adults ≥18 years with type 1 diabetes receiving basal and mealtime insulin for ≥1 year with HbA1c ≥7.0 and ≤10.0 % (≥53 and ≤86mmol/mol) at screening were included.
Exclusion criteria	Unstable insulin dose (±20 % total basal insulin dose) in the previous 30 days; use of premixed insulin, human regular insulin as mealtime insulin and/or any antihyperglycaemic drugs other than basal insulin and mealtime rapid-acting insulin analogues within 3 months; use of an insulin pump within 6 months; any contraindication for use of insulin glargine as defined by the product labelling in Japan; severe hypoglycaemia resulting in coma/seizures or hospitalization for diabetic ketoacidosis within 6 months
Method of allocation	Participants were randomized (1 : 1) to Gla-300 or Gla-100, stratified by HbA1c at screening visit [<8.0 or ≥8.0 % (<64 or ≥64mmol/mol)]. Owing to differences between insulin injection devices and injection volumes, the study was open-label; however, efficacy variables were assessed based on anonymized samples at the central laboratory.
Intervention(s)	Glargine U300 Participants received once-daily subcutaneous injections of Gla-300 [using a modified TactiPen® injector (Haselmeier GmbH, Zürich, Switzerland)] at the same time each evening (between pre-dinner and bedtime). The initial daily dose of Gla-300 or Gla-100 was equal to the total daily basal insulin dose on the day preceding the baseline visit for those previously receiving Gla-100 (once or twice daily), NPH insulin or insulin detemir once daily, or 20 % less for those previously receiving NPH insulin or insulin detemir more than once daily. Gla-300 or Gla-100 was titrated to a fasting (preprandial) self-monitored plasma glucose (SMPG) target of 4.4–7.2mmol/l (80–130mg/dl). Basal insulin dose titration was performed once weekly, and no more than every 3–4 days when more frequent adjustments were required. Participants continued mealtime insulin during the study, administered according to approved labelling in Japan and titrated to achieve glycaemic control after basal insulin doses had been optimized; mealtime dose could be reduced while basal insulin doses were increased to avoid daytime hypoglycaemia.

Comparator	Glargine U100 Participants received once-daily subcutaneous injections of Gla-100 [using a SoloSTAR® injector (Sanofi)] at the same time each evening (between pre-dinner and bedtime). The initial daily dose of Gla-300 or Gla-100 was equal to the total daily basal insulin dose on the day preceding the baseline visit for those previously receiving Gla-100 (once or twice daily), NPH insulin or insulin detemir once daily, or 20 % less for those previously receiving NPH insulin or insulin detemir more than once daily. Gla-300 or Gla-100 was titrated to a fasting (preprandial) self-monitored plasma glucose (SMPG) target of 4.4–7.2mmol/l (80–130mg/dl). Basal insulin dose titration was performed once weekly, and no more than every 3–4 days when more frequent adjustments were required. Participants continued mealtime insulin during the study, administered according to approved labelling in Japan and titrated to achieve glycaemic control after basal insulin doses had been optimized; mealtime dose could be reduced while basal insulin doses were increased to avoid daytime hypoglycaemia.
Outcome measures	**HbA1c** Change in HbA1c (%) % of participants achieving HbA1c <7.0% **Hypoglycaemia** Hypoglycaemia (all) - no. of participants experiencing ≥1 hypoglycaemic events over 6 months. Defined as symptomatic hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL]) Severe hypoglycaemia - no. of participants experiencing ≥1 hypoglycaemic events over 6 months. Nocturnal hypoglycaemia no. of participants experiencing ≥1 hypoglycaemic events over 6 months. Defined as events occurring between 00:00 -05:59 **Adverse events** Adverse events- related to treatment Serious adverse events- treatment emergent **Injection site reactions** **Body weight** Change in body weight (kg)
Loss to follow up	The discontinuation rate was 4.1 % for the Gla-300 group: withdrew due to AEs (1), withdrew due to lack of efficacy (1), other reasons (3) The discontinuation rate was 3.3 % for the Gla-100 group: withdrew due to lack of efficiency (2), other reasons (2)

Study arms

Glargine U300 (N = 122) Glargine U300 once daily with meal time insulin
Glargine U100 (N = 121) Glargine U100 once daily with meal time insulin

Characteristics

Arm-level characteristics

	Glargine U300 (N = 122)	Glargine U100 (N = 121)
% Female		
Sample Size	n = 66 ; % = 54	n = 65 ; % = 54
Mean age (SD)		
Mean/SD	44.1 (13.9)	46.3 (15.3)
BMI		
Mean/SD	23.8 (3.9)	23.2 (3.3)
Weight (kg)		
Mean/SD	63.9 (11.6)	61 (11.8)
Duration of diabetes (years)		
Mean/SD	12.2 (8.6)	13.9 (9)
HbA1c (%)		
Mean/SD	8.06 (0.64)	8.07 (0.74)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information on allocation concealment and randomisation.)

Cochrane Risk of Bias Tool 2.0		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open label trial could have influenced reporting of subjective outcomes (e.g. adverse events))
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No information on allocation concealment and randomisation. Open label trial could have influenced reporting of subjective outcomes (e.g. adverse events))
	Overall Directness	Partially applicable (Study does not specify which bolus insulins were used by the participants.)

Matsuhisa 2016b

Matsuhisa, 2016	
Bibliographic Reference	Matsuhisa, Munehide; Koyama, Masayoshi; Cheng, Xi; Sumi, Mariko; Riddle, Matthew C; Bolli, Geremia B; Hirose, Takahisa; EDITION JP 1 study, group; Sustained glycaemic control and less nocturnal hypoglycaemia with insulin glargine 300U/mL compared with glargine 100U/mL in Japanese adults with type 1 diabetes (EDITION JP 1 randomised 12-month trial including 6-month extension).; Diabetes research and clinical practice; 2016; vol. 122; 133-140

Study details

Study type	Randomised controlled trial (RCT) Extension trial of Matsuhisa 2016 A.
Trial registration number	NCT01689129
Study location	Japan
Study setting	22 centres in Japan
Study dates	October 2013 to October 2013
Duration of follow-up	12 months
Sources of funding	Study funded by Sanofi.
Sample size	243
Inclusion criteria	See Matsuhisa 2015 A
Exclusion criteria	See Matsuhisa 2015 A
Intervention(s)	Glargine U300 Once daily with mealtime insulin See Matsuhisa 2016 for further details.
Comparator	Glargine U100 Once daily with mealtime insulin See Matsuhisa 2016 for further details.
Outcome measures	**HbA1c** Change in HbA1c (%) **Hypoglycaemia** Hypoglycaemia (all) - Defined as symptomatic hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL]) Severe hypoglycaemia Nocturnal hypoglycaemia Defined as events occurring between 00:00 -05:59 **Adverse events** Adverse events- related to treatment **Injection site reactions** **Body weight** Change in weight (kg)

Loss to follow up	
Additional comments	Study is a 6 month extension of Matsuhisa 2016 A. During this trial participants continued randomised basal insulin treatment with less intensive follow-up.

Study arms

Glargine U300 (N = 122) Glargine U300 once daily with meal time insulin
Glargine U100 (N = 121) Glargine U100 once daily with meal time insulin

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information on allocation concealment and randomisation)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Some concerns (Open label trial could have influenced reporting of subjective outcomes (e.g. adverse events))
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No information on allocation concealment and randomisation. Open label trial could have influenced reporting of subjective outcomes (e.g. adverse events))
	Overall Directness	Partially applicable (Study does not specify which bolus insulins were used by the participants.)

Onda 2016

Onda, 2016

Bibliographic Reference	Onda, Yoshiko; Nishimura, Rimei; Ando, Kiyotaka; Takahashi, Hiroshi; Tsujino, Daisuke; Utsunomiya, Kazunori; Comparison of glycemic variability in Japanese patients with type 1 diabetes receiving insulin degludec versus insulin glargine using continuous glucose monitoring: A randomized, cross-over, pilot study.; Diabetes research and clinical practice; 2016; vol. 120; 149-55

Study details

Study type	Crossover randomised controlled trial
Study location	Japan
Study setting	Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine
Study dates	Not reported
Duration of follow-up	4 weeks
Sources of funding	Japan Diabetes Foundation
Sample size	13
Inclusion criteria	Treated on a basal-bolus insulin regimen received insulin therapy with frequent insulin injections for P12 weeks and were receiving insulin analogues as bolus insulin HbA1c >6.9% but <9% Being treated with diet therapy Age 20 - 80 years
Exclusion criteria	Patients had type 2 diabetes, were receiving oral hypoglycaemic agents, they had serious ketoacidosis or diabetic coma, serious infections, had undergone/were undergoing surgery or had serious traumatic injury, they had hepatic or renal impairment , severe cardiovascular or pulmonary disease, or any other condition or disease associated with hypoxia, they were in a state of malnutrition, starvation or debility or pituitary malnutrition or had adrenal dysfunction, they were habitual heavy drinkers, they were dehydrated or had gastrointestinal symptoms, they had malignancy, they had allergy to insulin or similar drugs or they were pregnant or likely to become pregnant
Method of allocation	All patients in either group were subjected to evaluation by CGM for glucose variability after 4 or more weeks of treatment with the first insulin formulation, and then were crossed over to the other insulin formulation immediately after completion of the first round of CGM assessments, and again subjected to CGM assessment for glucose variability after 4 or more weeks of treatment,
Intervention(s)	Degludec (concentration unknown) Once daily Prior to the start of the study, all patients received twice-daily subcutaneous injections of insulin glargine or insulin detemir as long-acting soluble insulin. When switching between insulin formulations, glargine was given at the same dose as that prior to the study, while degludec was given at a dose 10% less than the long-acting insulin dose given prior to the study to avoid episodes of unexpected hypoglycaemia. The insulin dose was not altered if fasting glucose levels remained below 110 mg/dL. Fast-acting insulin analogues were used as bolus insulin and administered as before the start of the study, with the insulin dose kept as close as possible to that before the start of the study.

Comparator	Glargine (concentration not known) Twice daily Prior to the start of the study, all patients received twice-daily subcutaneous injections of insulin glargine or insulin detemir as long-acting soluble insulin. When switching between insulin formulations, glargine was given at the same dose as that prior to the study, while degludec was given at a dose 10% less than the long-acting insulin dose given prior to the study to avoid episodes of unexpected hypoglycaemia. The insulin dose was not altered if fasting glucose levels remained below 110 mg/dL. Fast-acting insulin analogues were used as bolus insulin and administered as before the start of the study, with the insulin dose kept as close as possible to that before the start of the study.
Outcome measures	**Time in hypoglycaemia (< 70mg/dL) during 24 hours (mins)**
Additional comments	12 participants were already being given glargine prior to the study. No information about a washout or titration period

Study arms

Degludec (N = 13) Degludec (concentration unknown) Once daily Insulin degludec with pre-trial bolus insulin. Followed by cross-over to glargine with pre-trial bolus insulin
Glargine (N = 13) Glargine (concentration unknown) Twice daily Insulin glargine with pre-trial bolus insulin. Followed by cross-over to degludec with pre-trial bolus insulin

Characteristics

Study-level characteristics

	Study (N =)
% Female	
Nominal	46.1
Mean age (SD) (years)	
Mean/95% CI	44.9 (41 to 48.8)
Mean duration of diabetes (years)	
Mean/95% CI	15.5 (11.7 to 19.3)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation or allocation concealement)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High (No evidence of a washout or titration period)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns (No information about statistical tests for carry-over)
Overall bias and Directness	Risk of bias judgement	High (Limited information about randomisation and allocation concealement. No information about statistical tests for carry-over, results are grouped rather than reported by period, and most participants were already using one of the insulins before the trial started)
	Overall Directness	Partially applicable (Concentration of glargine and degludec not specified. Bolus insulin not specified.)

Pettus 2019

Pettus, 2019

Bibliographic Reference	Pettus, J.; Gill, J.; Paranjape, S.; Stewart, J.; Malla, S.; Edelman, S.; Bergenstal, R.M.; Bode, B.; Efficacy and safety of a morning injection of insulin glargine 300 units/mL versus insulin glargine 100 units/mL in adult patients with type 1 diabetes: A multicentre, randomized controlled trial using continuous glucose monitoring; Diabetes, Obesity and Metabolism; 2019; vol. 21 (no. 8); 1906-1913

Study details

Study type	Randomised controlled trial (RCT)
Trial registration number	NCT02688933
Study location	USA
Study setting	104 centres in the USA
Study dates	May 2016 to June 2017
Duration of follow-up	16 weeks
Sources of funding	Funded by Sanofi
Sample size	638
Inclusion criteria	• Aged ≥18 to ≤70 years at screening. Diagnosed with T1D ≥1 year prior to screening. On a stable dose of basal insulin analogue plus mealtime insulin for ≥1 year prior to screening. Had a daily basal insulin analogue dose of ≤80 units within 30 days of screening
Exclusion criteria	Fasting C-peptide ≥0.3 nmol/L. Using <2 mealtime injections of rapid-acting insulin analogue/day or using regular human insulin as mealtime insulin within 30 days prior to screening. Using any basal insulin other than a long-acting basal insulin analogue in the 3 months prior to screening. Using an insulin pump during the 6 months prior to screening. History of unstable diabetic retinopathy or other rapidly progressive retinopathy likely to require treatment during the study period. Pregnant or breast-feeding women or those planning pregnancy during the study duration. Patients who, during screening, were unable to use CGM appropriately or were non-compliant with SMBG
Method of allocation	Patients underwent a 4 week screening and CGM training period. During the screening and baseline training period, patients wore a blinded CGM device (Dexcom G4 Platinum Professional CGM, Dexcom, San Diego, California) for seven consecutive days. To be eligible for randomization, at least 4 days, not necessarily consecutive, of evaluable CGM data were required. Patients satisfying the inclusion criteria and CGM requirements were randomly assigned 1:1 to self-perform morning injection of Gla-300 or Gla-100, maintaining a consistent injection time. Randomization was stratified by baseline HbA1c (<8.0% vs ≥8.0% [<64 vs ≥64 mmol/mol]), frequency of basal insulin injection at screening (twice daily vs once daily), current use of CGM (yes/no) and mealtime insulin titration algorithm used (carbohydrate counting vs simple titration).
Intervention(s)	Glargine U300 Once daily (morning injections). Mealtime rapid-acting insulin analogues that had been used for at least 30 days prior to the screening visit were continued. Injections of Gla-100 or Gla-300 were delivered using a pen device that allowed dose-setting in the range of 1–80 units in 1-unit increments; the initiation dose on Day 1 of the treatment period was equal to the patients' current basal insulin dose. Patients performed self monitoring of blood glucose (SMBG) during the entire treatment period, with a fasting plasma glucose (FPG) target of 80–100 mg/dL (4.4–5.6 mmol/L), and the dose of Gla-300 or Gla-100 was titrated based on mean three-day fasting SMBG (without hypoglycaemia) using the titration algorithm provided

Comparator	Glargine U100 Once daily (morning injections). Mealtime rapid-acting insulin analogues that had been used for at least 30 days piror to the screening visit were continued. Injections of Gla-100 or Gla-300 were delivered using a pen device that allowed dose-setting in the range of 1–80 units in 1-unit increments; the initiation dose on Day 1 of the treatment period was equal to the patients' current basal insulin dose. Patients performed self monitoring of blood glucose (SMBG) during the entire treatment period, with a fasting plasma glucose (FPG) target of 80–100 mg/dL (4.4–5.6 mmol/L), and the dose of Gla-300 or Gla-100 was titrated based on mean three-day fasting SMBG (without hypoglycaemia) using the titration algorithm provided
Outcome measures	**HbA1c** Change in HbA1c (%) % of participants achieving HbA1c >7% **Hypoglycaemia** Hypoglycaemia (all)- symptomatic hypoglycaemia (≤70 mg/dL (≤3.9 mmol/L) Severe hypoglycaemia Nocturnal hypoglycaemia Nocturnal hypoglycaemia defined as an event with typical symptoms of hypoglycaemia acompanied by SMPG ≤70 mg/dL [3.9 mmol/L] occurring between 00:00 and 05:59 AM. **Adverse events** Adverse events- no. of patients with at least one treatment emergent AE. Serious AE - no. of patients with at least one serious treatment emergent AE. **Injection site reactions** **% time spent in target glucose range** Target range of 70–180 mg/dL (3.9–10.0 mmol/L),
Loss to follow up	Glargine U300 - reasons for discontinuation: adverse event (3), lack of efficacy (2), poor compliance (7), loss to follow up (1), hypoglycaemia (2), other reasons (14) Glargine U100 - reasons for discontinuation: adverse event (1), lack of efficacy (2), poor compliance (4), loss to follow up (5), hypoglycaemia (0), other reasons (25)
Limitations	Participants only wore CGM device for 7 days

Study arms

Glargine U300 (N = 320) Once daily with rapid mealtime insulin
Glargine U100 (N = 318) Once daily with rapid mealtime insulin

Characteristics

Arm-level characteristics

	Glargine U300 (N = 320)	Glargine U100 (N = 318)
% Female		
Sample Size	n = 140 ; % = 44	n = 138 ; % = 43
Mean age (SD)		
Mean/SD	45.5 (14)	45.5 (13.9)
BMI		
Mean/SD	27.5 (4.9)	27.7 (4.9)
Weight (kg)		
Mean/SD	81 (17.2)	81.4 (17)
Duration of diabetes		
Mean/SD	22.6 (13.1)	22.8 (13.4)
HbA1c (%)		
Mean/SD	8.01 (0.82)	7.99 (0.82)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information on allocation concealment and randomisation. Additionally, participants underwent 2 week screening programme prior to randomisation.)

Cochrane Risk of Bias Tool 2.0		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open lave trial could have potentially influenced subjective outcomes (e.g. adverse events))
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No information on allocation concealment and randomisation. Addtionally, participants underwent 2 week screening programme prior to randomisation. Open lave trial could have potentially influenced subjective outcomes (e.g. adverse events).)
	Overall Directness	Partially applicable (Study does not specify which bolus insulins were used by the participants.)

Pieber 2005

Pieber, 2005

Bibliographic Reference	Pieber, T R; Draeger, E; Kristensen, A; Grill, V; Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin.; Diabetic medicine : a journal of the British Diabetic Association; 2005; vol. 22 (no. 7); 850-7

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	7 European countries
Study setting	23 centres
Study dates	Not reported
Duration of follow-up	16 weeks
Sources of funding	Novo Nordisk
Sample size	400
Inclusion criteria	Aged 18 years and above BMI 35 kg/m² History of Type 1 diabetes ≥1 year Treated on a basal-bolus insulin regimen For ≥ 2 months Total daily basal insulin requirement of 100 IU/day HbA1c 12%
Exclusion criteria	Other significant medical disorders Recurrent major hypoglycaemia Pregnant or breast-feeding women Hypoglycaemic unawareness
Method of allocation	People were randomised centrally to a basal-bolus regimen with IDet with either morning and pre-dinner or morning and bedtime, or to NPH morning and bedtime.
Intervention(s)	Detemir (Levemir®,100 U/ml) (Novo Nordisk A/S, Bagsværd, Denmark) either morning and pre-dinner or morning and bedtime. Aspart (NovoRapid®, 100 U/ml, Novo Nordisk A/S) was also administered before meals. Insulin was injected subcutaneously (basal insulin in the thigh or abdomen, Aspart in the abdomen). The starting dose of basal insulin was 70% of the person's previous NPH insulin dose. Blood glucose targets: 4.0–7.0 mmol/ l pre-breakfast, pre-dinner and at night and ≤10.0 mmol/ l postprandially)
Comparator	NPH (Isophane human insulin®, 100 IU/ml, Novo Nordisk A/S) morning and bedtime. Aspart (NovoRapid®, 100 U/ml, Novo Nordisk A/S) was also administered before meals. Method of administration and blood glucose targets were the same as those used in the detemir arms

Outcome measures	**HbA1c** Change in HbA1c (%) - calculated using baseline and followup data. **Hypoglycaemia** Hypoglycaemia (all)- Hypoglycaemic episodes were classified as major (requiring assistance to treat), minor (glucsoe measurment <2.8 mmol/l) and symptoms only when a self-treated episodes was not confirmed by a glucose measurement. Major hypoglycaemia -Defined as requiring assistance to treat Nocturnal hypoglycaemia Defined as occurring between 23:00 to 06:00. **Body weight** Change in weight
Loss to follow up	In the two IDet groups, the reasons for withdrawal were: adverse events (n= 6), ineffective therapy(n= 3), non-compliance (n= 4) and personal reasons (n= 4). For the NPH group, all withdrawals were because of ineffectivetherapy (n= 4).
Additional comments	Evidence from the following arms were extracted: Detemir (morning+ bedtime) NPH (morning +bedtime)

Study arms

Detemir (morning and dinner) (N = 139) Insulin detemir in the morning and pre-dinner with pre-mealtime aspart Data not extracted for this arm
Detemir (morning and bedtime) (N = 132) Insulin detemir in the morning and at bedtime with pre-mealtime aspart
NPH (morning and bedtime) (N = 129) NPH insulin in the morning and at bedtime with pre-mealtime aspart

Characteristics

Arm-level characteristics

	Detemir (morning and dinner) (N = 139)	Detemir (morning and bedtime) (N = 132)	NPH (morning and bedtime) (N = 129)
% Female			
Nominal	43.9	31.8	43.4

	Detemir (morning and dinner) (N = 139)	Detemir (morning and bedtime) (N = 132)	NPH (morning and bedtime) (N = 129)
Age (years)			
Mean/SD	39 (12.4)	40.4 (11.4)	41.1 (11.9)
BMI (kg/m²)			
Mean/SD	25 (3.7)	25.4 (3.2)	25.2 (3.1)
HbA1c (%)			
Mean/SD	8.01 (1.24)	8.13 (1.37)	8.08 (1.15)
Basal insulin (IU/kg)			
Mean/SD	0.35 (0.14)	0.34 (0.13)	0.32 (0.13)
Mealtime insulin (IU/kg)			
Mean/SD	0.39 (0.17)	0.39 (0.17)	0.37 (0.14)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information about randomisation and allocation concealment.)
	Overall Directness	Directly applicable

Pieber 2007

Pieber, 2007

Bibliographic Reference	Pieber, T R; Treichel, H-C; Hompesch, B; Philotheou, A; Mordhorst, L; Gall, M-A; Robertson, L I; Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy.; Diabetic medicine : a journal of the British Diabetic Association; 2007; vol. 24 (no. 6); 635-42

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Germany, Austria and South Africa
Study setting	39 centres
Study dates	Not reported
Duration of follow-up	26 weeks
Sources of funding	Novo Nordisk
Sample size	322
Inclusion criteria	Aged 18 years and above BMI ≤35 kg/m² History of Type 1 diabetes For at least 1 year HbA1c 7.5% - 12.0%
Exclusion criteria	Proliferative retinopathy or maculopathy Recurrent major hypoglycaemia Pregnant or breast-feeding women Impaired hepatic or renal function Hypoglycaemic unawareness Cardiovascular disease
Intervention(s)	Insulin detemir (Levemir®; Novo Nordisk A/S, Sorgenfri, Denmark), twice-daily, at morning and bedtime. Insulin aspart (NovoRapid®; Novo Nordisk) was administered before main meals. Doses were adjusted aiming for a prebreakfast and pre-evening meal plasma glucose target of ≤7.3 mmol/l. Postprandial plasma glucose target (90 min after a meal) was ≤10.1 mmol/l
Comparator	Insulin glargine (Lantus®; Sanofi-Aventis, Paris, France), once daily, at bedtime. Insulin aspart (NovoRapid®; Novo Nordisk) was administered before main meals. Doses were adjusted aiming for a prebreakfast plasma glucose target of ≤7.3 mmol/l. Postprandial plasma glucose target (90 min after a meal) was ≤10.1 mmol/l

Outcome measures	**HbA1c** HbA1c (%) at follow up **Hypoglycaemia** Hypoglycaemia (all)- Defined as PG <3.1 mmol/l and no assistance required. Severe hypoglycaemia - Defined as assistance from a third party required. Nocturnal hypoglycaemia Nocturnal hypoglycaemic episodes was defined as episodes ocurring between 23:00 and 06:00h. **Adverse events** Serious adverse events- probably/ possibly related to treatment **Body weight** Change in weight (kg)
Loss to follow up	Detemir - withdrawn due to : adverse events (3), ineffective therapy (0), non-compliance (5), and other (6) Glargine - withdrawn due to : adverse events (1), ineffective therapy (5), non-compliance (4), and other (5)

Study arms

Detemir (N = 161) Twice-daily insulin detemir with premeal insulin aspart
Glargine (N = 161) Glargine U100 Once-daily insulin glargine with premeal insulin aspart

Characteristics

Arm-level characteristics

	Detemir (N = 161)	Glargine (N = 161)
% Female		
Nominal	45.34	52.2
Age (years (mean, range))		
Custom value	40 (18-79)	41 (18-70)
BMI (kg/m² (mean, range))		
Custom value	25.6 (18.2-35.1)	25.5 (16.8-34.4)
HbA1c (% (mean, range))		

	Detemir (N = 161)	Glargine (N = 161)
Custom value	8.9 (7.6-11.9)	8.8 (7.6-11.9)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Patient-reported adverse events may have been affected by open label trial design. Low risk for HbA1c and hypoglycaemia)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (For adverse events (patient-reported outcomes in open-label trial). Low risk for HbA1c and hypoglycaemia.)
	Overall Directness	Directly applicable

Pieber 2000

Pieber, 2000	
Bibliographic Reference	Pieber, T.R.; Eugene-Jolchine, I.; Derobert, E.; Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes; Diabetes Care; 2000; vol. 23 (no. 2); 157-162

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Europe
Study setting	42 centres
Study dates	Not reported
Duration of follow-up	4 weeks
Sources of funding	None reported
Sample size	333
Inclusion criteria	History of Type 1 diabetes Treated on a basal-bolus insulin regimen For at least 1 year
Exclusion criteria	Proliferative retinopathy or maculopathy Impaired hepatic or renal function Hypoglycaemic unawareness
Method of allocation	After a screening phase (7-14 days) patients were randomised to one of three treatment groups for the 4-week treatment phase.
Intervention(s)	1. HOE 901 30. Glargine with zinc concentration 30 ug/ml, injected into the abdomen once per day, between 9 and 11 pm. Regular human insulin also given before meals. Fasting plasma glucose target was 4-7 mmol/l without nocturnal hypoglycaemia 2. HOE 901 80. Glargine with zinc concentration 80 ug/ml, injected into the abdomen once per day, between 9 and 11 pm. Regular human insulin also given before meals. Fasting plasma glucose target was 4-7 mmol/l without nocturnal hypoglycaemia
Comparator	NPH insulin (once or twice daily) injected into the abdomen, between 9 and 11 pm. Regular human insulin also given before meals. Fasting plasma glucose target was 4-7 mmol/l without nocturnal hypoglycaemia
Outcome measures	**HbA1c** Change in HbA1c (%) Hypoglycaemia **Hypoglycaemia (all)** Severe hypoglycaemia Episodes of hypoglycaemia (2.8 mmol/l) were recorded by the patients and were classified as symptomatic, asymptomatic, and severe (requiring assistance) Nocturnal hypoglycaemia **Adverse events** **Injection site reactions**

Additional comments	Committee highlight that Lantus (glargine) contains 27-33 mcg/ml zince concentration. Based on this information the committee noted that glargine 80mcg/ml is not relevant to clincial practice as it is not currently available.

Study arms

Glargine (30) (N = 110) Glargine U100 Includes (30 µg/ml) once per day with mealtime regular human insulin
Glargine (80) (N = 113) Includes (80 µg/ml) once per day with mealtime regular human insulin. Data from this arm will not be used.
NPH (N = 110) NPH insulin once or twice daily with mealtime regular human insulin

Characteristics

Arm-level characteristics

	Glargine (30) (N = 110)	Glargine (80) (N = 113)	NPH (N = 110)
% Female			
Nominal	44	34	38
Age (years (mean, range))			
Custom value	35.6 (18-68)	37.5 (19-70)	35.7 (20-61)
BMI (kg/m² (mean, range))			
Custom value	24.0 (18.7-28.3)	24.0 (18.6-30.3)	24.0 (18.9-29.1)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation or allocation concealment)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Limited information about statistical methods)

Cochrane Risk of Bias Tool 2.0		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (No information about missing outcome data)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (For hypoglycaemia and adverse events (patient reported in open label trial). Low risk for HbA1c)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns (Limited information about statistical analysis)
Overall bias and Directness	Risk of bias judgement	Some concerns (Insufficient information about randomisation and statistical analysis.)
	Overall Directness	Partially applicable (Glargine formulation included zinc.)

Porcellati 2004

Porcellati, 2004	
Bibliographic Reference	Porcellati, F; Rossetti, P; Pampanelli, S; Fanelli, C G; Torlone, E; Scionti, L; Perriello, G; Bolli, G B; Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin.; Diabetic medicine : a journal of the British Diabetic Association; 2004; vol. 21 (no. 11); 1213-20

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Italy
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	52 weeks
Sources of funding	National Ministry of Scientific Research and University of Perugia
Sample size	121
Inclusion criteria	History of Type 1 diabetes Treated on a basal-bolus insulin regimen multiple daily combinations of lispro and NPH insulin at each meal, and NPH at bedtime, for at least 2 years Free of any detectable microangiopathic complication and were negative at the screening for autonomic neuropathy
Exclusion criteria	Not reported
Intervention(s)	4 x daily Continuation of lispro and NPH insulin at each meal, and NPH at bedtime for 1 year. Blood glucose targets: 6.4–7.2 mmol/ l (115–130 mg/dl) in the fasting state, before meals and at bedtime. 8.0–9.2 mmol/l (145–165 mg/dl) 2 h after meals
Comparator	Glargine U100 once daily Administration of insulin glargine (Lantus®, Aventis Pharmaceutical, purchased from Hostato Apotheke, Frankfurt, Germany) at dinner-time (20.00 h) with mealtime lispro, for 1 year. Blood glucose targets were the same as those used in the NPH arm
Outcome measures	**Hypoglycaemia** Frequency of hypoglycaemia (all) - episodes/ patient- month Defined as hypoglycaemia was defined as any episode associated with measurement of blood glucose ≤ 4.0 mmol/ l(72 mg/dl) irrespective of symptoms. Severe hypoglycaemia - no. of patients Defined as episode requiring external help. Nocturnal hypoglycaemia Frequency of nocturnal hypoglycaemia - episodes/ patient- month Nocturnal episodes of hypoglycaemia were calculated from values measured at 03.00 h or any time between 01.00 and 07.30 h when participants awoke with symptoms suggestive of hypoglycaemia.

Study arms

NPH (N = 60) 4 X daily NPH at mealtimes and bedtime, with mealtime lispro
Glargine (N = 61) Once daily Insulin glargine at dinnertime, with mealtime lispro

Characteristics

Arm-level characteristics

	NPH (N = 60)	Glargine (N = 61)
% Female		
Nominal	45	55.7
Age (years)		
Mean/SD	34 (1)	36 (1)
BMI (kg/m²)		
Mean/SD	23.2 (0.15)	22.9 (0.14)
HbA1c (%)		
Mean/SD	7.1 (0.2)	7.1 (0.1)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Open label trial but outcomes were objective)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Cochrane Risk of Bias Tool 2.0		
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Partially applicable (NPH was given 4 times daily.)

Raskin 2000

Raskin, 2000	
Bibliographic Reference	Raskin, P; Klaff, L; Bergenstal, R; Halle, J P; Donley, D; Mecca, T; A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes.; Diabetes care; 2000; vol. 23 (no. 11); 1666-71

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	USA and Canada
Study setting	Multicentre (60 centres)
Study dates	October 1997 and July 1998
Duration of follow-up	12 weeks
Sources of funding	Study was supported by Hoechst Marion Roussel.
Sample size	619
Inclusion criteria	People with type 1 diabetes, aged 18-80 years, and had been receiving treatment with NPH insulin with at least 1 year and insulin lispro for at least 3 months. Patients had to have a serum C-peptide level ≤9mg/dl (0.5mmol/l)in the presence of a blood glucose level ≥99.0mg/dl (5.5mmol/l) and a Ghb value ≤12.0%.
Exclusion criteria	Patients with hepatic or renal impairment, those who were pregnant or breast feeding, and those who received treatment with any glucose-lowering drug other than insulin within 4 weeks of the study.
Method of allocation	After the screening phase, patients were stratified on the basis of their prior regimen of NPH insulin: once a day or more than once a day.
Intervention(s)	Glargine U100 Supplied in vails containing 5ml solution (1 mil containing 100 U insulin). Insulin lispro was supplied in vials containing 10 ml solution (1 ml containing 100 U insulin).
Comparator	NPH Supplied in vials containing 10 ml suspension (1 ml containing 100 U insulin). Insulin lispro was supplied in vials containing 10 ml solution (1 ml containing 100 U insulin).

Outcome measures	**HbA1c** Change in HbA1c (%)- calculated using GHb (%) at follow up and baseline **Hypoglycaemia** Hypoglycaemia (all) Severe hypoglycaemia Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia in which the subject required assistance from another person and which was accompanied by a blood glucose level <36.0 mg/dl (2.0 mmol/l) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. Nocturnal hypoglycaemia Nocturnal hypoglycaemia was defined as that occurring while the subject was asleep during the time between bedtime after the evening injection and before getting up in the morning (i.e., before morning determination of fasting blood glucose and morning injection). **Adverse events** Adverse events - treatment related events **Injection site reactions** (pain, haemorrhage and mass)
Loss to follow up	A total of 31 patients, 15 in the insulin glargine group and 16 in the NPH insulin group, withdrew from the study before the end of the treatment phase; most of these patients either wanted to discontinue study participation or were lost to follow-up.

Study arms

Glargine (N = 310) Glargine U100 Once-daily insulin glargine with mealtime insulin lispro
NPH (N = 309) NPH insulin either once or twice per day with mealtime insulin lispro

Characteristics

Arm-level characteristics

	Glargine (N = 310)	NPH (N = 309)
% Female		
Nominal	49.4	47.6
Age (years)		
Mean/SD	38.9 (12.2)	39.5 (12.2)
BMI (kg/m²)		
Mean/SD	25.5 (3.4)	25.7 (3.9)
HbA1c (%)		
Mean/SD	7.6 (1.2)	7.7 (1.2)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Adverse events - patient reported outcomes in an open label trial. Low risk for HbA1c and hypoglycaemia (objective outcomes).)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Adverse events - patient reported outcomes in an open label trial. Low risk for HbA1c and hypoglycaemia)
	Overall Directness	Directly applicable

Ratner 2000

Ratner, 2000

Bibliographic Reference	Ratner, R E; Hirsch, I B; Neifing, J L; Garg, S K; Mecca, T E; Wilson, C A; Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes.; Diabetes care; 2000; vol. 23 (no. 5); 639-43

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Multicentre (49 sites)
Study dates	Not specified
Duration of follow-up	28 weeks
Sources of funding	Study was supported by a research grant from Hoechst Mario Roussel.
Sample size	534
Inclusion criteria	Men and women 18-80 years of age with type 1 diabetes (post prandial C-peptide levels of ≤0.5nmol/l) for at least 1 year and GHb levels of ≤12.0%.
Exclusion criteria	Treatment with antidiabetic drugs other than insulin within 1 month of study entry, pregnancy, impaired hepatic function, and impaired renal function. Subjects could not work a night shift.
Intervention(s)	Glargine U100 Once daily (at bedtime) Subjects in the insulin glargine group were to be switched from once-daily NPH insulin on a unit-for-unit basis, whereas a slight dose decrease was recommended for subjects who switched from twice-daily NPH insulin. Subjects used regular insulin ~30 mins before meals to meet prandial insulin requirements.
Comparator	NPH Once daily (at bedtime) or twice daily (at bedtime and before breakfast) depending on their pretreatment insulin regimens. Subjects used regular insulin ~30 mins before meals to meet prandial insulin requirements.
Outcome measures	**HbA1c** Change in HbA1c (%)- Calculated using baseline and follow up data. **Hypoglycaemia** Hypoglycaemia (all) - Defined as blood glucose <2.0 mmol/l Severe hypoglycaemia - Defined as requiring the assistance of another individual. Nocturnal hypoglycaemia Defined as occurring while asleep after bedtime insulin dose and before the morning capillary FBG measurement. **Adverse events** Adverse events Serious AEs- possibly related to treatment **Injection site reactions**

Loss to follow up	Early discontinuation: 11.7% in glargine arm, 8.1% in NPH arm A total of 8 subjects (3%) in the insulin glargine group discontinued the regimen because of adverse events, 3 of which were considered possibly related to treatment. One subject receiving NPH insulin discontinued the regimen because of an adverse event, that was not considered to be related to the study medication.
Additional comments	Dose titration of both basal insulins was based on capillary fasting blood glucose (FBG) levels; the goal was a premeal blood glucose concentration of 4.4–6.7 mmol/l (80–120 mg/dl). Dose increases were made if morning capillary FBG levels were consistently >6.7 mmol/l with no symptomatic nocturnal hypoglycaemia.

Study arms

Glargine (N = 264)

Glargine U100 Once daily (at bedtime). Subjects used regular insulin ~30 mins before meals to meet prandial insulin requirements.

NPH (N = 270)

Once daily (at bedtime) or twice daily (at bedtime and before breakfast) depending on their pretreatment insulin regimens. Subjects used regular insulin ~30 mins before meals to meet prandial insulin requirements.

Characteristics

Arm-level characteristics

	Glargine (N = 264)	NPH (N = 270)
% Female		
Sample Size	n = 123 ; % = 46.6	n = 141 ; % = 52.2
Mean age (SD)		
Mean/SD	38.2 (12.2)	38.9 (11.9)
BMI		
Mean/SD	25.63 (4.01)	25.93 (4.55)
Diabetes duration (years)		
Mean/SD	17.9 (11.66)	16.9 (10)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information on allocation and randomisation process.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (Last observation carried forward' used to adjust for missing data.)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No information on allocation and randomisation process. Potential bias introduced due to adjustment of missing data)
	Overall Directness	Directly applicable

Renard 2011

Renard, 2011	
Bibliographic Reference	Renard, Eric; Dubois-Laforgue, Daniele; Guerci, Bruno; Variability Study, Group; Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability in type 1 diabetes patients: a multicenter, randomized, crossover study.; Diabetes technology & therapeutics; 2011; vol. 13 (no. 12); 1213-8

Study details

Study type	Crossover randomised controlled trial
Study location	France
Study setting	25 diabetes care centres
Study dates	Not reported
Duration of follow-up	16 weeks
Sources of funding	Sanofi-Aventis
Sample size	88
Inclusion criteria	History of Type 1 diabetes For more than 3 years, defined by a C-peptide concentration of < 0.1 nmol/L and a fasting blood glucose (FBG) ‡ 7 mmol/L. Treated on a basal-bolus insulin regimen For at least 6 months with glargine as basal insulin HbA1c ≤8.5%
Exclusion criteria	Not reported
Method of allocation	Patients continued their current insulin treatment for 1–2 weeks and then received glulisine as prandial insulin (three times per day) for an initial period of 4 weeks. Then, patients with a more than 50% of pre-dinner blood glucose (PDBG) level of £ 8.3 mmol/L during the last 3 weeks of the initial period were randomized in two crossover groups using insulin glargine or insulin detemir. Each crossover period lasted 16 weeks, without washout between both periods.
Intervention(s)	Once-daily glargine, given as an evening injection (period 1), followed by once- (evening) or twice (pre-breakfast and evening) detemir (period 2). Both were given with mealtime insulin gluisine. Blood glucose targets were: (1) fasting and before meals, 5.0 mmol/L < blood glucose £ 7.2 mmol/L; (2) 1–2 h after meal starting, blood glucose < 9.9 mmol/L; and (3) at bedtime (at least 2.5 h after the last meal), 6.1 mmol/L ≤blood glucose £ 8.3 mmol/L
Comparator	Once- (evening) or twice (pre-breakfast and evening) detemir (period 2), followed by once-daily glargine, given as an evening injection (period 1). Both were given with mealtime insulin gluisine. Blood glucose targets were the same for both arms

Outcome measures	**HbA1c** Change in HbA1c (%) - Study reports change in GHb (%) **Hypoglycaemia** Severe hypoglycaemia Severe hypoglycaemia was defined as an episode in which the patient's condition requires the indispensable assistance of a third person and is associated with blood glucose of < 1.98 mmol/L or a quick recovery after ingestion of sugar or intravenous glucose or glucagon administration. Nocturnal hypoglycaemia **Adverse events** Adverse event (related to basal insulin) Serious adverse events
Loss to follow up	Glargine/ Detemir: withdrawn (5), dropped out (2), adverse event (2), protocol violation (1) Detemir/ Glargine: withdrawn (3), dropped out (2), adverse event (1)
Limitations	The randomization was skewed because of the fact that it was organized per investigation centre. As a consequence, it happened that in the centres that randomized few patients the allocation to glargine (first period)/detemir (second period) or detemir (first period)/glargine (second period) was not balanced. The difference between this trial distribution (50:38) and a balanced one (44:44) was not statistically significant.

Study arms

Glargine (N = 50) Glargine U100 Once-daily glargine followed by once- or twice-daily detemir. Both with mealtime glulisine
Detemir (N = 38) Once-or twice-daily detemir followed by once-daily glargine. Both with mealtime glulisine

Characteristics

Arm-level characteristics

	Glargine (N = 50)	Detemir (N = 38)
Age (years)		
Mean/SD	48.3 (13.6)	46.4 (14.1)
% Female		
Nominal	34.1	44.1

	Glargine (N = 50)	Detemir (N = 38)
BMI (kg/m²)		
Mean/SD	24.6 (3.5)	25.3 (3.5)
HbA1c (%)		
Mean/SD	7.06 (0.69)	7.16 (0.71)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High (Limited information about randomisation or allocation concealment. This paper presents data from the extension phase of a 12 month study. the number of participants is not equally balanced between the groups and there is no information about period effects.)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Some concerns (No washout period)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns (Low for HbA1c and hypoglycaemia. Some concerns for adverse events - patient-reported outcome in open-label trial)
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns (Limited information about statistical analysis)
Overall bias and Directness	Risk of bias judgement	High (Limited information about randomisation and allocation concealment. Imbalances in the number of participants in each arm of the trial, no washout period and no evidence of a statistical test for carryover or period analysis)
	Overall Directness	Directly applicable

Rosenstock 2000

Rosenstock, 2000

Bibliographic Reference	Rosenstock, J; Park, G; Zimmerman, J; U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator, Group; Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group.; Diabetes care; 2000; vol. 23 (no. 8); 1137-42

Study details

Study type	Randomised controlled trial (RCT) Partially double-blind randomised trial
Study location	USA
Study setting	Multicentre
Study dates	Not specified
Duration of follow-up	4 weeks
Sample size	257
Inclusion criteria	People with type 1 diabetes, aged between 18 and 70 years of age and had a BMI of 18-28kg/m2, HbA1c of <10%, and postprandial serum C-peptide of <0.2pmol/ml. All study patients had been on a basal-bolus multiple daily insulin regimen for at least 2 months.
Exclusion criteria	Not reported
Intervention(s)	Glargine U100 (30) - Glargine with 30 µg/ml zinc chloride Glargine U100 (80) - Glargine with 80 µg/ml zinc chloride 2 formulations of glargine were studied to investigate the effect of zinc on the clinical response to insulin glargine. Insulin glargine was given by subcutaneous abdominal injection once daily at bedtime. The initial dose of either formulation of insulin glargine was to be equal to the total daily dose of NPH insulin the patient was using at the time of randomisation to treatment. Injections of regular insulin were administered 30 mins before meals according to the patients' usual practice.
Comparator	NPH NPH insulin was given as a subcutaneous abdominal injection either once daily (at bedtime) or twice daily (before breakfast and at bedtime) based on the patient's prestudy treatment regimen. NPH insulin contained 100 U/ml recombinant human insulin. Injections of regular insulin were administered 30 mins before meals according to the patients' usual practice.

Outcome measures	**HbA1c** Change in HbA1c (%) **Hypoglycaemia** Hypoglycaemic (all) Hypoglycaemia was categorised as follows: Symptomatic: symptoms of hypoglycaemia reported by the patient that may have been confirmed by a blood glucose level <2.8 mmol/l Severe: symptomatic hypoglycaemia in which routine activities were curtailed or assistance was required; this may have been confirmed by a blood glucose level <2.8 mmol/l or the prompt recovery of the patient after administration of oral carbohydrate, intravenous glucose, or glucagon Nocturnal: occurring between bedtime basal insulin and FBG determination the next morning Asymptomatic: blood glucose or plasma glucose level <2.8 mmol/l, with no symptoms
Loss to follow up	One patient who was assigned to the NPH treatment group and lost to follow ip, did not complete the study.

Study arms

Glargine (30) (N = 82) Glargine U100 Once daily at bedtime. Injections of regular insulin were administered 30 mins before meals according to the patients' usual practice.
Glargine (80) (N = 86) Glargine U100 Once daily at bedtime. Injections of regular insulin were administered 30 mins before meals according to the patients' usual practice.
NPH (N = 88) NPH insulin contained 100 U/ml. Given either once daily (at bedtime) or twice daily (before breakfast and at bedtime). Injections of regular insulin were administered 30 mins before meals according to the patients' usual practice.

Characteristics

Arm-level characteristics

	Glargine (30) (N = 82)	Glargine (80) (N = 86)	NPH (N = 88)
% Female			
Sample Size	n = 40 ; % = 48.8	n = 42 ; % = 48.8	n = 41 ; % = 46.6
Mean age (SD)			
Mean/SD	37.5 (11.7)	37 (11.5)	37.9 (12.5)
BMI			
Mean/SD	23.9 (2.5)	24.4 (2.5)	24.5 (2.7)

	Glargine (30) (N = 82)	Glargine (80) (N = 86)	NPH (N = 88)
Duration of diabetes (year)			
Mean/SD	16.7 (11.3)	15.8 (10)	16.3 (10.8)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information on allocation and randomisation process.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No information on allocation concealment and randomisation.)
	Overall Directness	Partially applicable (Glargine formulations include zinc.)

Rossetti 2003

Rossetti, 2003

Bibliographic Reference	Rossetti, Paolo; Pampanelli, Simone; Fanelli, Carmine; Porcellati, Francesca; Costa, Emanuela; Torlone, Elisabetta; Scionti, Luciano; Bolli, Geremia B; Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month

	comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime.; Diabetes care; 2003; vol. 26 (no. 5); 1490-6

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Not specified
Study dates	Not specified
Duration of follow-up	3 months
Sources of funding	Financial support obtained from National Ministry of Scientific Research and the University of Perugia.
Sample size	51
Inclusion criteria	People with type 1 diabetes and fasting plasma C-peptide ≤0.15 nmol/l on intensified treatment with multiple daily combinations of lispro and NPH insulin at each meal and NPH at bedtime.
Exclusion criteria	Not specified
Method of allocation	After a 15-day run-in period during which previous insulin treatment was continued, the patients were randomized to either continuation of the lispro and NPH combinations at each meal and NPH at bedtime, administration of insulin glargine at dinnertime, and administration of insulin glargine at bedtime for 3 months. NPH doses at each meal were adjusted based on preprandial blood glucose values. Mealtime doses of lispro were 0.04 – 0.08 units/kg at breakfast and 0.10 – 0.17 units/kg at lunch and dinner. The lispro doses were adjusted daily on the basis of preprandial blood glucose, blood glucose 2 h after meals of previous days, as well as composition and size of meals and physical activity.
Intervention(s)	1. Glargine U100 (dinnertime) 2. Glargine U100 (bedtime) Given once a day Mealtime lispro insulin was continued. Insulin glargine was always injected alone without previous mixing with lispro. For the first 2 days of treatment, the daily glargine doese was assumed to identical to the total daily NPH units of the run-in period. Afterwards, the odse of glargine was varied by 1-2 units every 2-3 days, if necessary, to meet the target fasting blood glucose. Mealtime doses of lispro were 0.04 – 0.08 units/kg at breakfast and 0.10 – 0.17 units/kg at lunch and dinner. The lispro doses were adjusted daily on the basis of preprandial blood glucose, blood glucose 2 h after meals of previous days, as well as composition and size of meals and physical activity.
Comparator	NPH Given 4 times a day Mealtime lispro insulin was continued With syringes, lispro and NPH insulins were mixed and immediately injected. The ratio of lispro to NPH was 70/30 at breakfast, 60/40 at lunch and 90/10 at dinner. The bedtime NPH dose was 0.2 units/kg.

Outcome measures	**HbA1c** Change in HbA1c (%) - calculated using baseline and follow up data. **Hypoglycaemia** Frequency of mild hypoglycaemia Severe hypoglycaemia - no. of patients Hypoglycaemia was defined as any episode associated with measurement of blood glucose ≤4.0 mmol/l irrespective of symptoms. Hypoglycaemia was considered mild when the episodes were self treated by the patients and severe when the episode required any kind of external help. Nocturnal hypoglycaemia Frequency of nocturnal hypoglycaemia

Study arms

Glargine (dinnertime) (N = 17) Glargine U100 once a day. Mealtime lispro insulin was continued
Glargine (bedtime) (N = 17) Glargine U100 Once a day. Mealtime lispro insulin was continued
NPH (N = 17) 4 times a day. Mealtime lispro insulin was continued

Characteristics

Arm-level characteristics

	Glargine (dinnertime) (N = 17)	Glargine (bedtime) (N = 17)	NPH (N = 17)
% Female			
Sample Size	n = 9 ; % = 54.9	n = 7 ; % = 41.1	n = 8 ; % = 47.1
Mean age (SD)			
Mean/SD	31.3 (3.4)	34 (3.1)	32 (3)
BMI			
Mean/SD	22.9 (1)	23.2 (0.9)	23.1 (0.8)
Diabetes duration years			

	Glargine (dinnertime) (N = 17)	Glargine (bedtime) (N = 17)	NPH (N = 17)
Mean/SD	12.9 (2.3)	14.8 (2.3)	13.1 (1.9)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information on allocation and randomisation process.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Method of analysis to estimate the effect of assignment to intervention not specified in the study.)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (No information on allocation and randomisation process. Method of analysis to estimate the effect of assignment to intervention not specified in the study.)
	Overall Directness	Partially applicable (Insulin NPH was used 4 time daily.)

Russell -Jones 2004

Russell-Jones, 2004

Bibliographic Reference	Russell-Jones, David; Simpson, Richard; Hylleberg, Birgitte; Draeger, Eberhard; Bolinder, Jan; Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen.; Clinical therapeutics; 2004; vol. 26 (no. 5); 724-36

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Europe and Australia
Study setting	92 sites
Study dates	Not reported
Duration of follow-up	6 months
Sources of funding	Novo Nordisk
Sample size	749
Inclusion criteria	Aged 18 years and above History of Type 1 diabetes For over 1 year Treated on a basal-bolus insulin regimen Already using basal or premixed insulin QD in the evening (between 5 PM and 11 PM) and human insulin before meals for over 2 months
Exclusion criteria	Proliferative retinopathy or maculopathy Recurrent major hypoglycaemia Pregnant or breast-feeding women Impaired hepatic or renal function Severe cardiac problems Uncontrolled hypertension Poorly controlled diabetes HbA1c >12% and/or a total basal insulin dose >100 IU/d
Method of allocation	After a 3 week screening period, eligible patients were randomly assigned (2:1) to 6 months of treatment with either insulin detemir or NPH insulin QD at bedtime, using a computerised randomisation system.
Intervention(s)	Insulin detemir (100 U/mL) QD at bedtime. Bolus injections of human insulin (100 IU/mL) were administered with main meals for both treatments. All insulin preparations were supplied in 3.0-mL cartridges and were injected subcutaneously into the thigh or abdomen using an injection pen. Treatment included an initial 1-month titration period, during which dosing was optimized to meet individual requirements, and a 5-month maintenance period. Titration of basal insulin doses to optimum levels to achieve target self monitored blood glucose (SMBG) levels (prebreakfast/ night, 4.0–7.0 mmol/L [72–126 mg/dL]; 90 minutes postprandial, £10.0 mmol/L [180 mg/dL]) was recommended over the first 2 weeks.

Comparator	NPH insulin (100 IU/mL) QD at bedtime. Bolus injections of human insulin (100 IU/mL) were administered with main meals for both treatments. Administration methods, timing and blood glucose targets were the same as those in the detemir arm
Outcome measures	**HbA1c** Change in HbA1c (%) **Hypoglycaemia** Hypoglycaemia (all) A hypoglycaemic episode was classified as major if the patient was unable to self-treat, as minor if the blood glucose value was ,2.8 mmol/L (50 mg/dL) and the patient dealt with the episode alone, and as symptoms only if no assistance was required and the event was not confirmed by a blood glucose measurement. Major hypoglycaemia - Defined as patient unable to self-treat Nocturnal hypoglycaemia Defined as episodes occurring between 11pm and 6am. **Body weight** Change in weight
Loss to follow up	Withdrawals in detemir arm: adverse events (5), ineffective therapy (3), noncompliance (2), other (17) Withdrawals in NPH arm: adverse events (2), ineffective therapy (0), noncompliance (5), other (15)

Study arms

Detemir (N = 491) Insulin detemir at bedtime with bolus injections of human insulin
NPH (N = 256) NPH insulin at bedtime with bolus injections of human insulin

Characteristics

Arm-level characteristics

	Detemir (N = 491)	NPH (N = 256)
% Female		
Nominal	34.4	38.7

	Detemir (N = 491)	NPH (N = 256)
Age (years)		
Mean/SD	40.9 (12.4)	39.8 (12.3)
BMI (kg/m²)		
Mean/SD	25.1 (3.4)	25.4 (3.4)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Limited information about randomisation or allocation concealment)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (Open label trial due to clear differences in the two types of insulin)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Limited information about randomisation and allocation concealment.)
	Overall Directness	Directly applicable

Standl 2004

Standl, 2004

Bibliographic Reference	Standl, Eberhard; Lang, Hanne; Roberts, Anthony; The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes.; Diabetes technology & therapeutics; 2004; vol. 6 (no. 5); 579-88

Study details

Study type	Randomised controlled trial (RCT) Parallel RCT
Study location	Europe, Australia and New Zealand
Study setting	47 sites
Study dates	Not reported
Duration of follow-up	12 months
Sources of funding	Novo Nordisk
Sample size	461
Inclusion criteria	Aged 18 years and above 18-74 years BMI ≤35.0 kg/m² History of Type 1 diabetes For over 12 months Treated on a basal-bolus insulin regimen For at least 2 months Total daily basal insulin requirement of 100 IU/day HbA1c ≤12%
Exclusion criteria	Proliferative retinopathy or maculopathy Recurrent major hypoglycaemia Allergy to insulin Pregnant or breast-feeding women Impaired hepatic or renal function Severe cardiac problems Uncontrolled hypertension
Method of allocation	No information.
Intervention(s)	Insulin detemir twice daily, and human insulin (Actrapid ®, Novo Nordisk) before meals as subcutaneous injections using the NovoPen® 3 device (Novo Nordisk). Doses were adjusted continuously at investigators' discretion based on patients' self-measured BG (SMBG) measurements, aiming for the following targets: fasting, 4–7 mmol/L; 90-min postprandial, <10 mmol/L; at 0200 and 0400 a.m., 4–7 mmol/L

Comparator	NPH insulin (isophane human insulin, Novo Nordisk, Bagsvaerd, Denmark) twice daily, and human insulin (Actrapid ®, Novo Nordisk) before meals as subcutaneous injections using the NovoPen® 3 device (Novo Nordisk). Blood glucose targets were the same as those used in the detemir arm
Outcome measures	**HbA1c** Change in HbA1c (%) - Calculated using baseline and follow up data **Hypoglycaemia** Hypoglycaemia (all) Major hypoglycaemia Hypoglycaemia was defined as major if third party help was required, minor if blood glucose was below 2.8 mmol/L and the patient handled the episode him- or herself, and as symptoms only if not confirmed by BG measurement. **Adverse events** Adverse events - probably/possibly related to study medication **Injection site disorders**
Loss to follow up	Reasons given for noncompletion in the insulin detemir and NPH insulin groups, respectively, were: protocol violation (n =1; n =1), adverse events (n = 2; n = 0), ineffective therapy (n = 6; n = 8), non-compliance (n = 6; n = 2), and “other” (n = 6; n = 7)
Limitations	Study included a 6 month initial treatment phase followed by a 6 month extension phase. Those completing the initial 6 months were invited to participate in the 6-month extension period. This phase cannot be considered as randomised.
Additional comments	Of the 461 individuals enrolled into the study, 421 completed the initial 6-month treatment period: 212 on insulin detemir and 209 on NPH insulin. Of these, 289 continued into the extension period (154 on insulin detemir and 135 on insulin NPH). 134 in detemir arm and 118 in NPH arm completed the trial.

Study arms

Detemir (N = 154) Insulin detemir twice daily with human insulin at mealtimes
NPH (N = 134) NPH insulin twice daily with human insulin at mealtimes

Characteristics

Arm-level characteristics

	Detemir (N = 154)	NPH (N = 134)
Age (years)		
Mean/SD	40.7 (13.4)	42.5 (12.3)
% Female		
Nominal	38	34
BMI (kg/m²)		
Mean/SD	25.2 (3)	25.6 (3.3)
HbA1c (%)		
Mean/SD	7.72 (1.26)	7.66 (1.19)
Basal insulin dose (IU)		
Mean/SD	26.8 (11.7)	27.1 (12)
Bolus insulin dose (IU)		
Mean/SD	28.7 (13.8)	26 (9.5)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High (Limited information about randomisation and allocation concealement. Additonally, inital treatment phase was followed by an extension phase. This phase was not considered randomised.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (10% of people in detemir arm and 7% in NPH arm did not complete first 6 months of the trial)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open label trial - subjective outcomes (adverse events) could have been influenced by knowledge of intervention)

Cochrane Risk of Bias Tool 2.0		
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High (Limited information about randomisation and allocation concealement. Additonally, inital treatment phase was followed by an extension phase. This phase was not considered randomised. Subjective outcomes (adverse events) may have been affected by open-label trial design)
	Overall Directness	Directly applicable

Vague 2003

Vague, 2003	
Bibliographic Reference	Vague, Philippe; Selam, Jean-Louis; Skeie, Svein; De Leeuw, Ivo; Elte, Jan W F; Haahr, Hanne; Kristensen, Allan; Draeger, Eberhard; Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart.; Diabetes care; 2003; vol. 26 (no. 3); 590-6

Study details

Study type	Randomised controlled trial (RCT)
Study location	46 investigational sites in Europe
Study setting	Hospital setting
Duration of follow-up	6 months
Sources of funding	Trial was sponsored by Novo Nordisk.
Sample size	447
Inclusion criteria	Patients with a history of type 1 diabetes for at least 1 year who had received basal (once or multiple daily) bolus insulin treatment for at least 2 months. Patients with HbA1c level less than or equal to 12%, a BMI less than or equal to 35kg/m2, and a total basal insulin dosage of less than or equal to 100 IU/day.
Exclusion criteria	Pregnant or breast-feeding women Patients with proliferative retinopathy, impaired hepatic or renal function, severe cardiac problems, uncontrolled hypertension, recurrent major hypoglycaemia, or allergy to insulin.
Method of allocation	After a 3 week screening period patients were randomised (in a 2:1 ratio) to insulin detemir or NPH insulin. Randomisation was performed using a telephone randomisation system, the interactive voice response system.
Intervention(s)	Detemir Patients were instructed to administer detemir (1,200 nmol/ml) before breakfast and bedtime and aspart before each main meal as subcutaneous injections using the NovoPen 3 device. During the first 2 weeks, basal insulin doses were optimised following instructions of the investigator based on the patients' self-measured blood glucose profiles. In the following weeks, the dose ratio between rapid- acting and basal insulin was adjusted.
Comparator	NPH Patients were instructed to administer NPH (600 nmol/ml) before breakfast and bedtime and aspart before each main meal as subcutaneous injections using the NovoPen 3 device. During the first 2 weeks, basal insulin doses were optimised following instructions of the investigator based on the patients' self-measured blood glucose profiles. In the following weeks, the dose ratio between rapid- acting and basal insulin was adjusted.

Outcome measures	**HbA1c** Change in HbA1c (%) -calculated using baseline and follow up data. **Hypoglycaemia** Hypoglycaemia (all) Major hypoglycaemia Hypoglycaemic episodes were classified as as “major” if assistance to treat was required, minor if blood glucose was below 2.8 mmol/L and the patients dealt with the episode themselves, and as symptoms if not confirmed by BG measurement. Nocturnal hypoglycaemia Defined as occurring between 23:00 to 06:00 **Adverse events** **Injection site reactions** **Body weight** Change in weight - calculated using baseline and follow up data.
Loss to follow up	Detemir arm: Five patients were withdrawn: three patients because of ineffective therapy, noncompliance, and other reasons, respectively, and two patients because of adverse events NPH arm: Five patients were also withdrawn in the NPH insulin group: two patients because of ineffective therapy and three patients because of other reasons
Methods of analysis	HbA1c (reference range of assay, 4.0-6.0%) was determined by high-performance liquid chromatography.
Additional comments	The first month of the trial was regarded as a titration phase, whereas the last 5 months were considered the maintenance phase. Patients were instructed to aim for blood glucose targets (fasting/preprandial, 4 –7 mmol/l; postprandial, <10 mmol/l; from 0200 to 0400, 4–7mmol/l). They recorded insulin dose, concomitant medication, and hypoglycemia in diaries and were encouraged to measure blood glucose whenever symptoms of hypoglycaemia occurred.

Study arms

Detemir (N = 301) Patients were instructed to administer detemir (1,200 nmol/ml) before breakfast and bedtime and aspart before each main meal
NPH (N = 146) Patients were instructed to administer NPH (600 nmol/ml) before breakfast and bedtime and aspart before each main meal

Characteristics

Arm-level characteristics

	Detemir (N = 301)	NPH (N = 146)
% Female		
Sample Size	n = 139 ; % = 46.2	n = 72 ; % = 49.3
Mean age (SD)		
Mean/SD	38.9 (13.3)	41.8 (14.2)
BMI		
Mean/SD	24.5 (3.2)	24.6 (3.4)
Diabetes duration		
Mean/SD	17.1 (9.9)	17.4 (11)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

Van Golen 2013

van Golen, 2013

Bibliographic Reference	van Golen, Larissa W; IJzerman, Richard G; Huisman, Marc C; Hensbergen, Jolanda F; Hoogma, Roel P; Drent, Madeleine L; Lammertsma, Adriaan A; Diamant, Michaela; Cerebral blood flow and glucose metabolism in appetite-related brain regions in type 1 diabetic patients after treatment with insulin detemir and NPH insulin: a randomized controlled crossover trial.; Diabetes care; 2013; vol. 36 (no. 12); 4050-6

Study details

Study type	Crossover randomised controlled trial
Trial registration number	NCT00626080
Study location	Netherlands
Study setting	Hospital setting
Study dates	January 2009 to May 2011
Duration of follow-up	12 weeks
Sources of funding	This work was supported by an investigator initiated grant of Novo Nordisk. Novo Nordisk supplied all insulin preparations.
Sample size	28
Inclusion criteria	Patients with type 1 diabetes, aged 18-60 years with a BMI of 18-35 kg/m2
Exclusion criteria	Diabetes duration <1 year; A1C >8.5%; proliferative retinopathy; a history of recurrent severe hypoglycaemia (defined as an episode that requires external assistance for recovery); a medical history of hypoglycaemia unawareness; history of cardiovascular, renal, or liver disease or severe head trauma; any neurological or psychiatric disorder; endocrine diseases not well controlled for the last 3 months; inability to undergo magnetic resonance imaging (MRI) scanning; substance abuse; and the use of anticoagulants, oral steroids, or any centrally acting agent.
Method of allocation	Randomisation (block design) was conducted by the trial pharmacy, and the assigned treatments were concealed by envelopes, a research physician enrolled patients in the study and assigned them to the intervention.
Intervention(s)	Detemir Patients were assigned to start detemir in the evening both in combination with insulin aspart at mealtimes. Where appropriate, basal insulin dose was adjusted to maintain a fasting glucose level of <7 mmol/L.
Comparator	NPH Patients were assigned to start NPH in the evening both in combination with insulin aspart at mealtimes. Where appropriate, basal insulin dose was adjusted to maintain a fasting glucose level of <7 mmol/L.
Outcome measures	**HbA1c** Change in HbA1c (%) - calculated using baseline and follow up data. **Body weight** Change in body weight (kg)
Loss to follow up	One participant dropped out during the first treatment period and one person dropped out in the second period.

Study arms

Detemir (N = 28) Patients were assigned to start detemir in the evening both in combination with insulin aspart at mealtimes
NPH (N = 28) Patients were assigned to start NPH in the evening both in combination with insulin aspart at mealtimes

Characteristics

Study-level characteristics

	Study (N = 28)
% Female	
Custom value	Not specified
Mean age (SD)	
Mean/SD	36.9 (9.7)
BMI	
Mean/SD	24.9 (2.7)
Diabetes duration	
MedianIQR	12.8 (6 to 17)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Some concerns (No information on washout period.)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns (Data for different phases not presented separately.)

Cochrane Risk of Bias Tool 2.0		
Overall bias and Directness	Risk of bias judgement	Some concerns (Washout period not specified. No information on test for carryover.)
	Overall Directness	Directly applicable

Witthaus 2001

Witthaus, 2001	
Bibliographic Reference	Witthaus, E; Stewart, J; Bradley, C; Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes.; Diabetic medicine : a journal of the British Diabetic Association; 2001; vol. 18 (no. 8); 619-25

Study details

Study type	Randomised controlled trial (RCT)
Study location	10 European counties
Study setting	Not specified
Study dates	Not specified
Duration of follow-up	28 weeks
Sources of funding	Study was sponsored, designed and managed by Aventis Pharma as part of the Phase III development progrmme for insulin glargine.
Sample size	517
Inclusion criteria	People with Type 1 diabetes with a minimum experience of one year of previous insulin use.
Exclusion criteria	Not specified
Intervention(s)	Glargine U100 Glargine was administered by subcutaneous injection once daily at bedtime. Dose adjustments for both insulins were targeted at a self-monitored pre-meal blood glucose concentration of 4.4-6.7 mmol/l (80-120mg/dl). In addition to glargine, regular insulin was administered before each meal. With the intention of standardising other aspects of treatment patients previously using insulin lispro were switched to regular human insulin
Comparator	NPH NPH human insulin was administered by subcutaneous injection either once or more than once, depending on the regimen followed prior to the study. Dose adjustments for both insulins were targeted at a self-monitored pre-meal blood glucose concentration of 4.4-6.7 mmol/l (80-120mg/dl). In addition to NPH, regular insulin was administered before each meal. With the intention of standardising other aspects of treatment patients previously using insulin lispro were switched to regular human insulin
Outcome measures	**QoL** Change from baseline to final assessment in the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) and Wellbeing Questionnaire (W-BQ) scores.
Loss to follow up	Not specified
Methods of analysis	An intention-to-treat analysis was performed, including all patients who were randomised and treated and who had completed both a pre-treatment and at least one on-treatment questionnaire.

Additional comments	The DTSQ is an 8-item questionnaire that measures satisfaction with diabetes treatment. Each of the eight items is scored on a scale from 0 to 6. The DTSQ generates a sum score for Treatment Satisfaction from Items 1, 4, 5, 6, 7, and 8 (with a possible minimum (maximum) score of 0 (36), and two individual item scores for Perceived Frequency of Hyperglycaemia and Perceived Frequency of Hypoglycaemia. The W-BQ22 is a 22-item questionnaire providing an overall measure of General Well-being (combining all 22 items) and is composed of four subscales: Depression (Items 1 - 6), Anxiety (Items 7 - 12), Energy (Items 13 - 16) and Positive Well-being (Items 17 - 22). Each of the 22 items is scored on a scale from 0 to 3, where 0 = not at all, and 3 = all the time. The W-BQ22 generates a sum score (0 – 66) and four subscale scores: Depression (0 – 18), Anxiety (0 – 18), Energy (0 – 12) and Positive Well-being (0 – 18). The DTSQ and W-BQ scales and subscales are scored in the direction of the scale or subscale label, i.e., an increase in the score signifies an increase in the label.

Study arms

Glargine (N = 261) Glargine U100 Glargine was administered by subcutaneous injection either once daily at bedtime. In addition to glargine, regular insulin was administered before each meal.
NPH (N = 256) NPH human insulin was administered by subcutaneous injection either once or more than once, depending on the regimen followed prior to the study. In addition to NPH, regular insulin was administered.

Characteristics

Arm-level characteristics

	Glargine (N = 261)	NPH (N = 256)
% Female		
Sample Size	n = 119 ; % = 45.6	n = 111 ; % = 43.4
Mean age (SD)		
Mean/SD	40.1 (12.31)	29.4 (11.9)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer

Cochrane Risk of Bias Tool 2.0		
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (Open label trial. Potential bias introduced for subjective outcomes.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Open label trial. Potential bias introduced for subjective outcomes.)
	Overall Directness	Directly applicable

Zachariah 2011

Zachariah, 2011	
Bibliographic Reference	Zachariah, Sunil; Sheldon, Ben; Shojaee-Moradie, Fariba; Jackson, Nicola C; Backhouse, Katharine; Johnsen, Sigurd; Jones, Richard H; Umpleby, A Margot; Russell-Jones, David L; Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes.; Diabetes care; 2011; vol. 34 (no. 7); 1487-91

Study details

Study type	Crossover randomised controlled trial
Trial registration number	NCT00509925
Study location	UK
Study setting	Hospital setting
Study dates	32 weeks (exact dates not reported)
Duration of follow-up	16 weeks
Sources of funding	Study supported by a grant from Novo Nordisk.
Sample size	23 people
Inclusion criteria	Patients with type 1 diabetes on a basal-bolus regimen Type 1 diabetes duration > 12 months, on basal-bolus insulin regimen for > 3 months, age >18 years, BMI <40 kg/m2, and HbA1c between 7.0 and 11.0%
Exclusion criteria	Anticipated change in medication known to interfere with glucose metabolism, proliferative retinopathy, recurrent major hypoglycaemia or hypoglycaemic unawareness, impaired hepatic or renal functions, pregnancy, and uncontrolled hypertension.
Method of allocation	Patients were randomly assigned to receive either insulin detemir or NPH insulin as a basal insulin. After 16 weeks of treatment, subjects were switched to the other basal insulin.
Intervention(s)	Insulin detemir Detemir was administered once (17 patients) or twice daily (5 patients), according to individual needs and pre-breakfast and predinner glucose targets (aiming for <6.0 mmol/L without significant hypoglycaemia). Insulin aspart was used throughout as the bolus insulin.
Comparator	NPH Insulin NPH was administered once or twice daily, according to individual needs and pre-breakfast and predinner glucose targets (aiming for <6.0 mmol/L without significant hypoglycaemia). Insulin aspart was used throughout as the bolus insulin.
Outcome measures	**HbA1c** Change in HbA1c (%) - calculated using baseline and follow up data. **Hypoglycaemia** Hypoglycaemia (all) - hypoglycaemic episodes Major hypoglycaemia - defined as unable to treat themselves. **Body weight** Change in weight (kg)
Loss to follow up	One patient did not complete the trial for personal reasons.

Study arms

Detemir (N = 22) Detemir was administered once (17 patients) or twice daily (5 patients), according to individual needs and pre-breakfast and predinner glucose targets (aiming for <6.0 mmol/L without significant hypoglycaemia). Insulin aspart was used throughout as the bolus insulin.
NPH (N = 22) NPH was administered once or twice daily, according to individual needs and pre-breakfast and predinner glucose targets (aiming for <6.0 mmol/L without significant hypoglycaemia). Insulin aspart was used throughout as the bolus insulin.

Characteristics

Study-level characteristics

	Study (N = 23)
% Female	
Sample Size	n = 9 ; % = 39
Mean age (SD)	
Mean/SD	38.8 (2.17)
BMI	
Mean/SD	28 (3.6)
Duration of diabetes	
Mean/SD	19.95 (2.09)

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Insufficient information on randomisation process.)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Some concerns (No information on washout period. Study also highlights that subjects knew they were on insulin detemir which has been known to cause less weight gain which might be a confounding factor.)
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low

Cochrane Risk of Bias Tool 2.0		
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns (No information on statistical test for carry-over. Data for different phases not presented separately.)
Overall bias and Directness	Risk of bias judgement	Some concerns (Insufficient information on randomisation process and washout period. No information on statistical test for carryover. Data for different phases not presented separately.)
	Overall Directness	Directly applicable

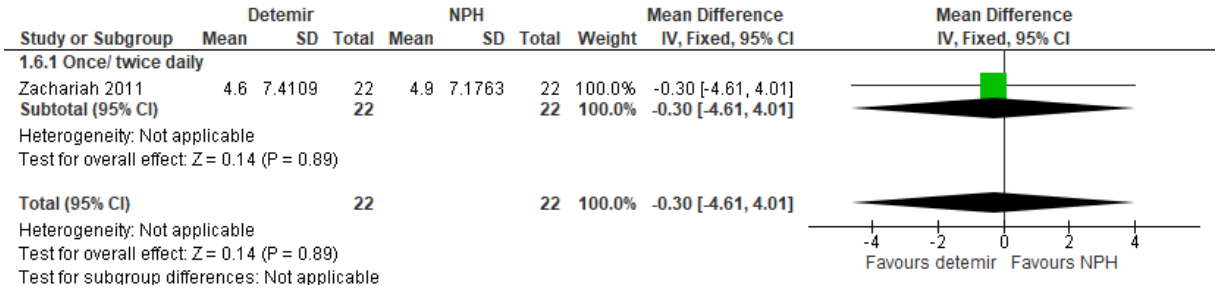
Appendix F – Forest plots

Forest plots below highlight findings for the outcomes not used in the NMA.

Detemir vs NPH

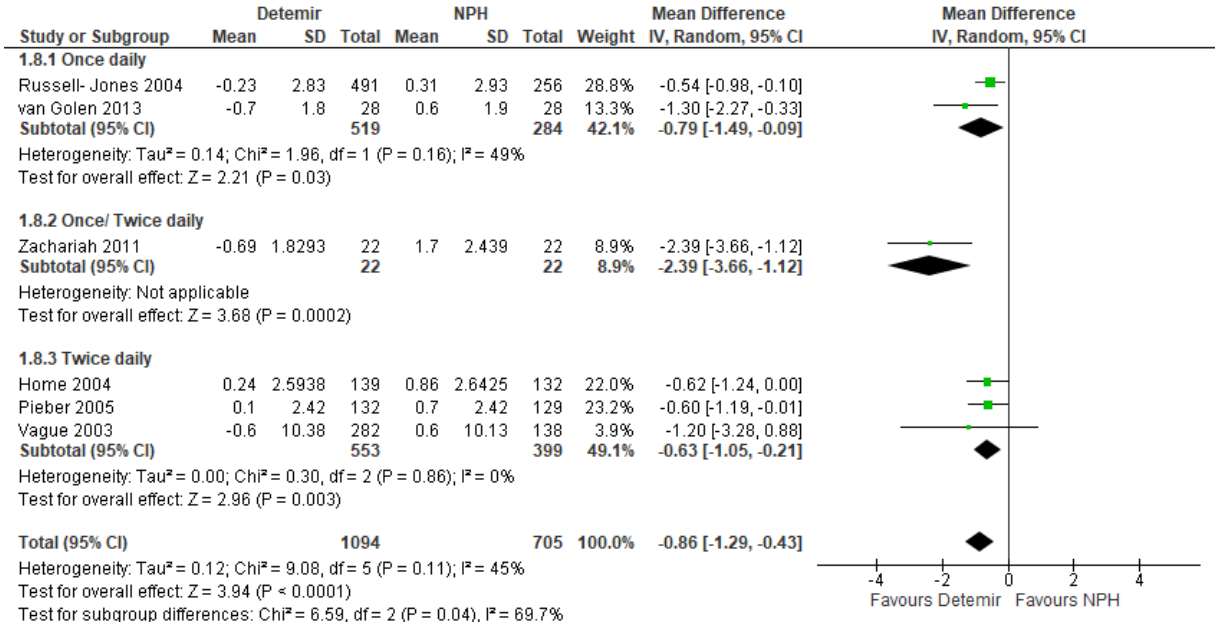
Outcomes ≤ 6 months

Hypoglycaemia episodes

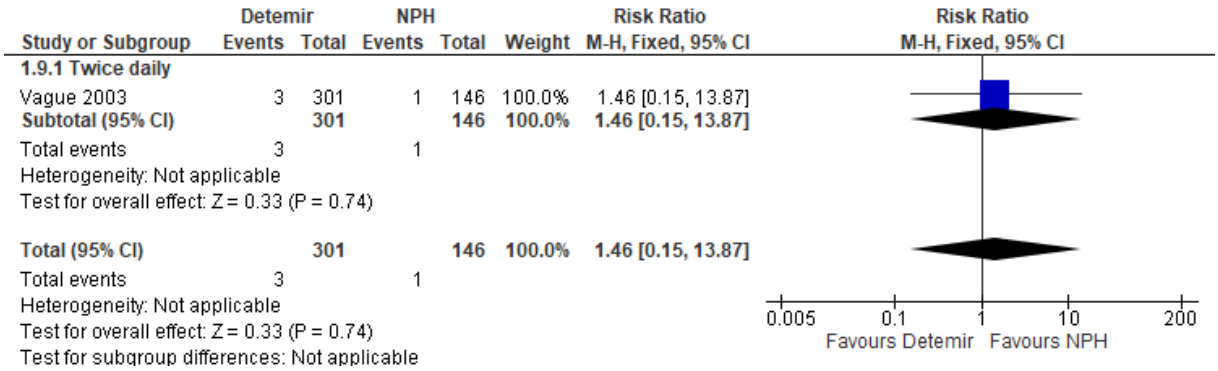


Change in weight (kg)

(MD less than 0 favours detemir)

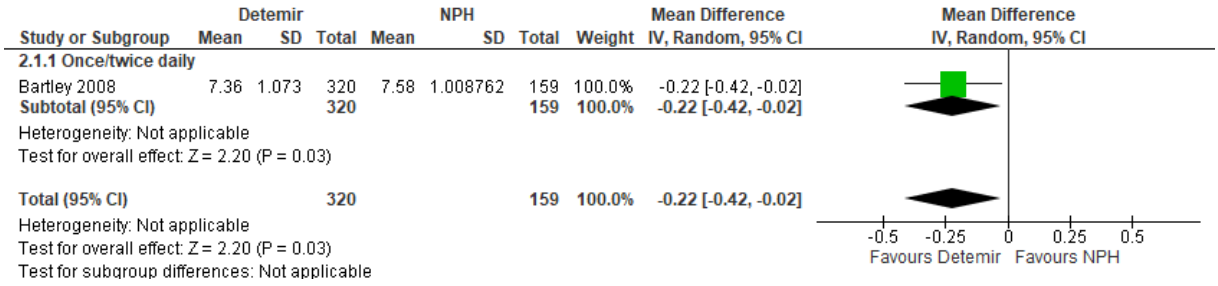


Injection site reactions

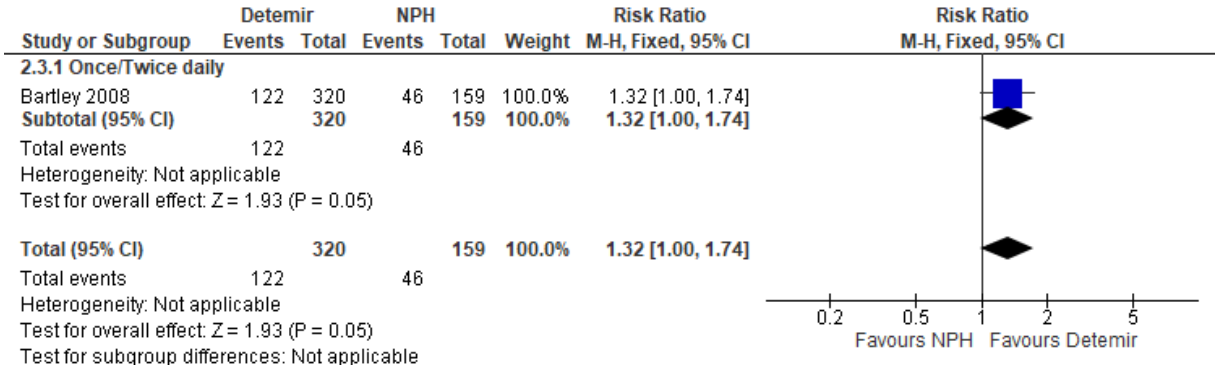


Outcomes > 6 months

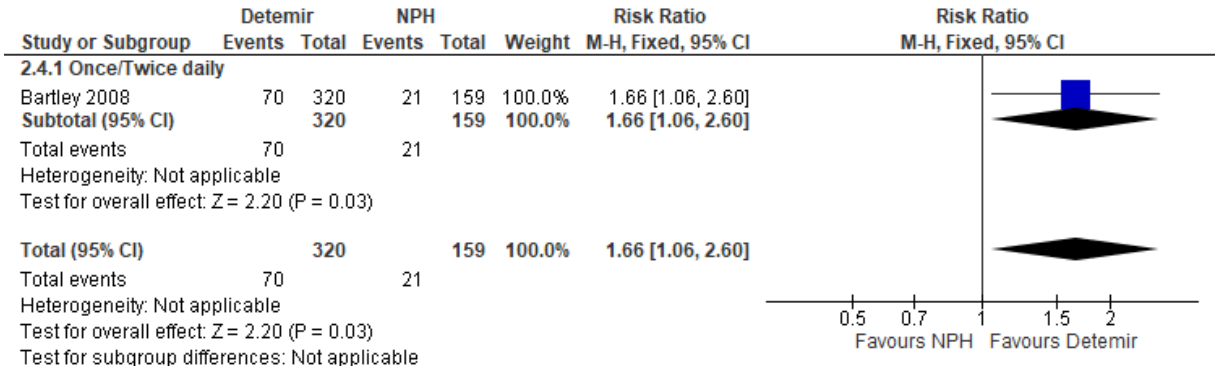
HbA1c (%) at follow up



Patients achieving HbA1c ≤ 7%

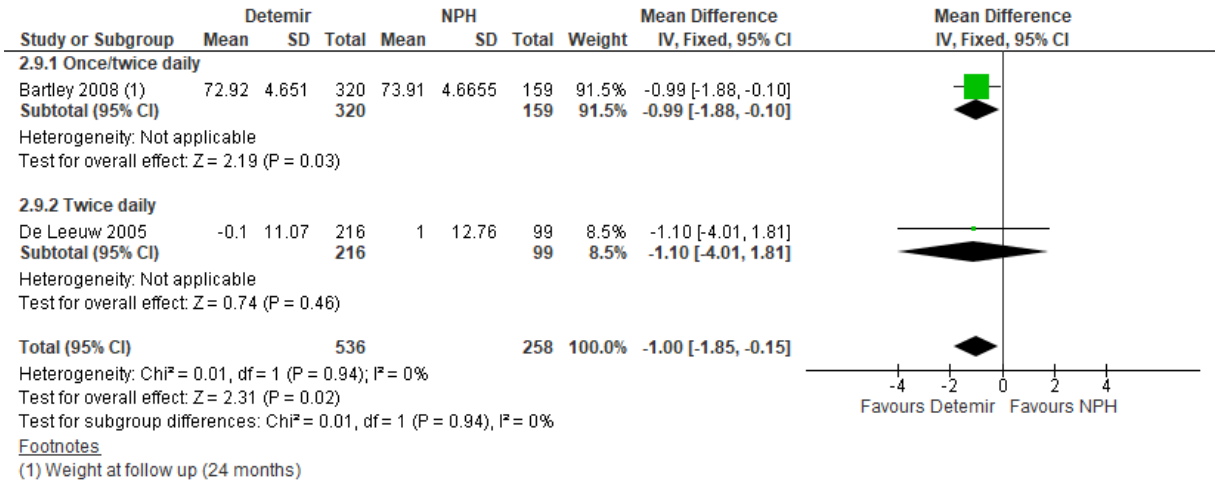


Patients achieving HbA1c ≤ 7% in the absence of confirmed hypoglycaemia

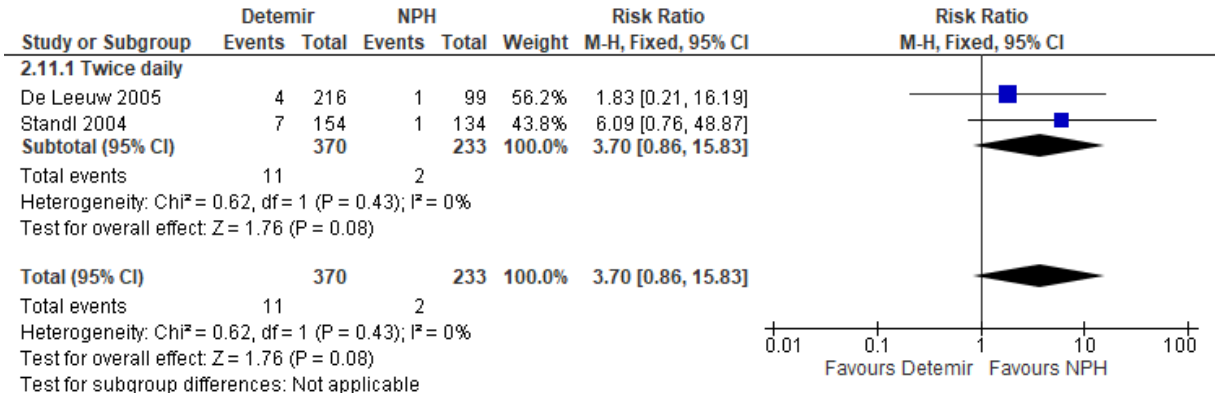


Change in weight (kg)

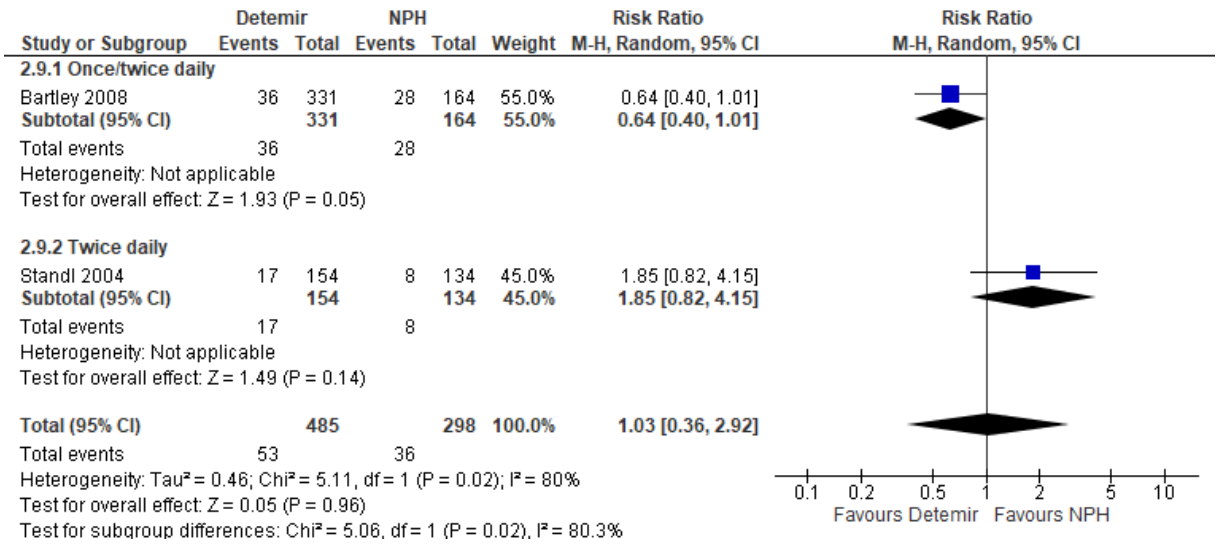
(MD less than 0 favours detemir)



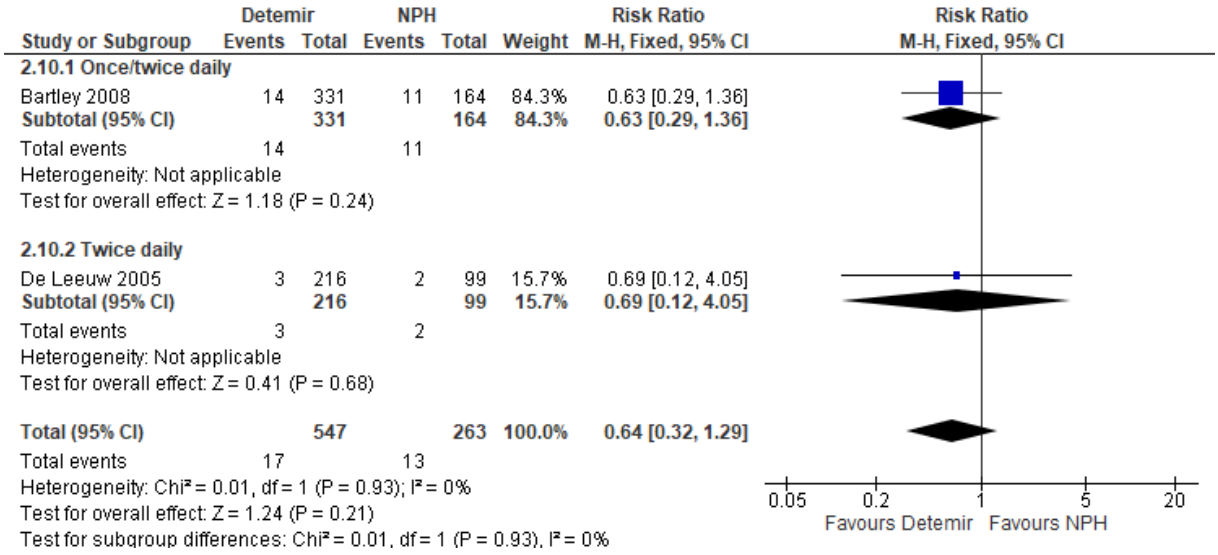
Injection site reactions



Adverse events



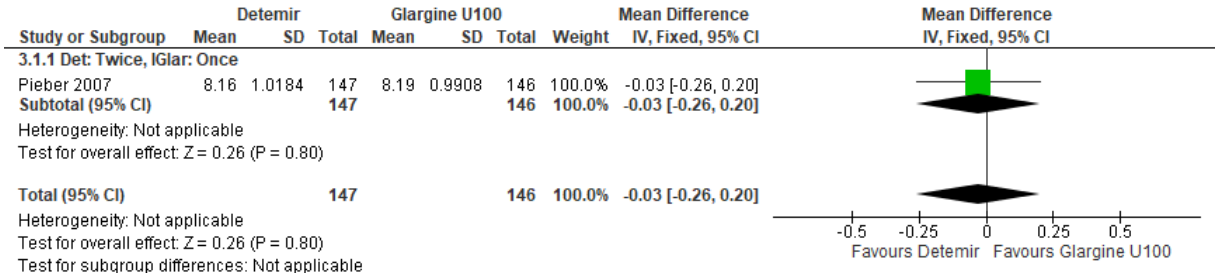
Serious AEs



Detemir vs Glargine U100

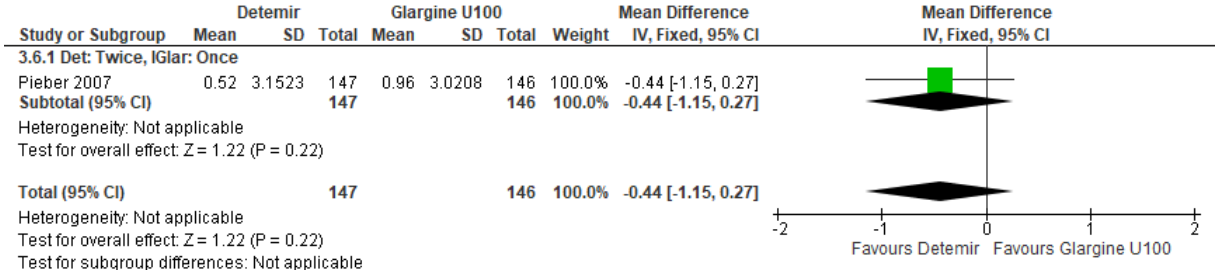
Outcomes ≤ 6 months

HbA1c (%) at follow up

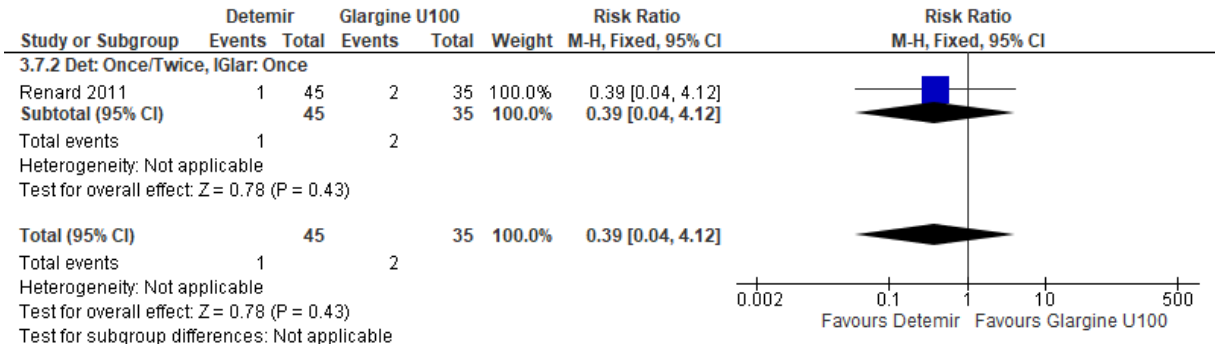


Change in weight (kg)

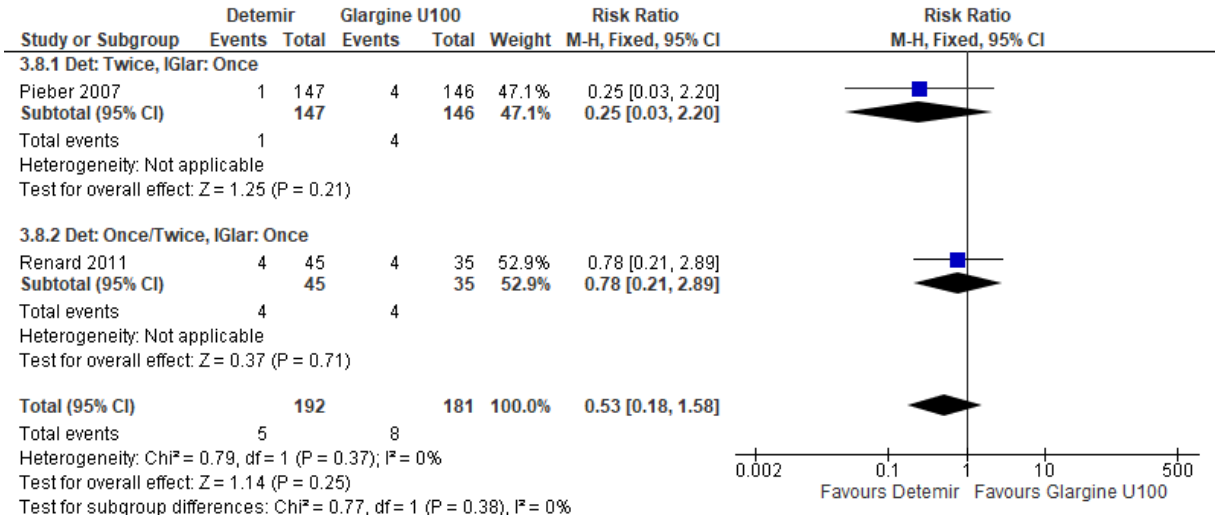
(MD less than 0 favours detemir)



Adverse events

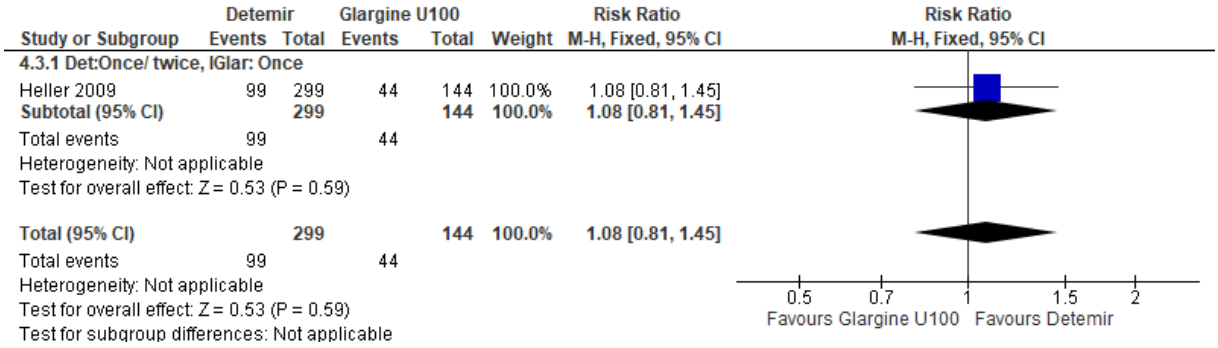


Serious AEs



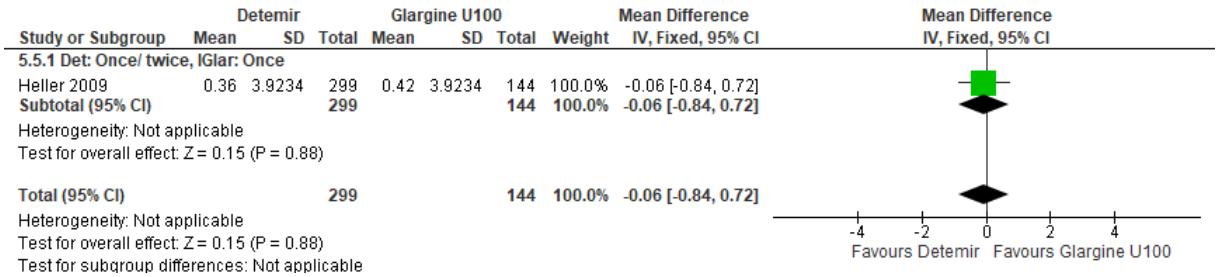
Outcomes > 6 months

Patients achieving HbA1c ≤ 7%

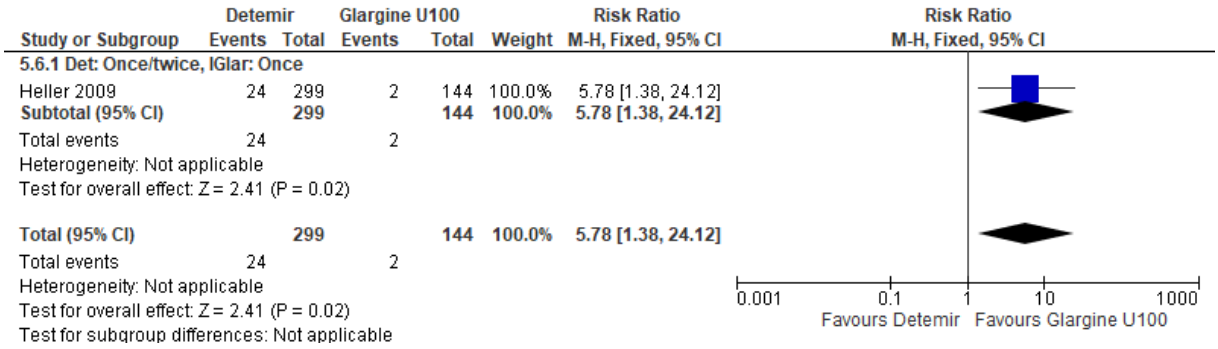


Change in weight (kg)

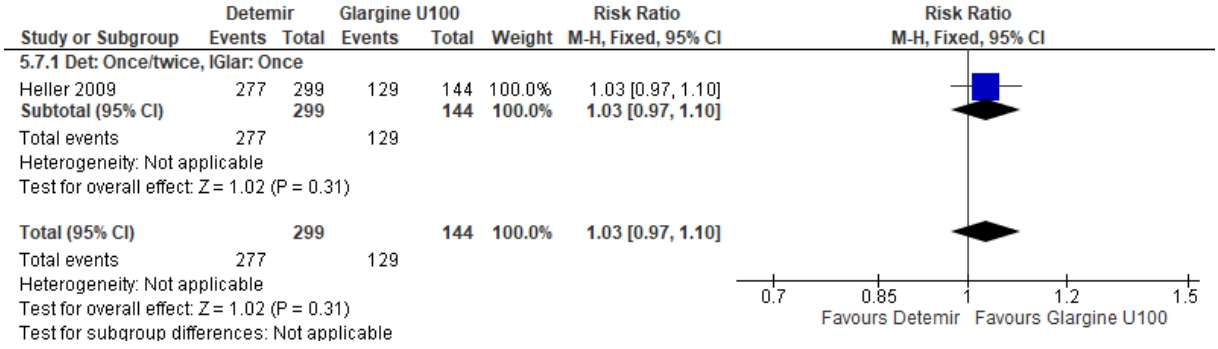
(MD less than 0 favours detemir)



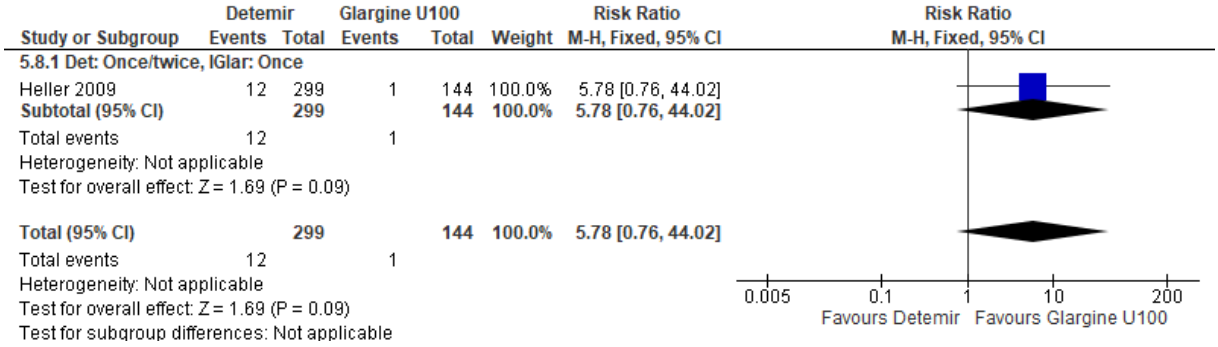
Injection site reactions



Adverse events



Serious AEs

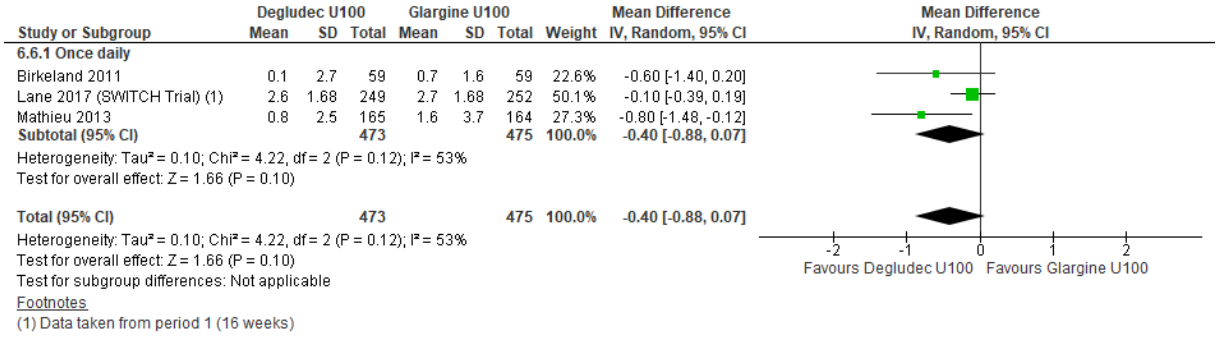


Degludec U100 vs Glargine U100

Outcomes ≤ 6 months

Change in weight (kg)

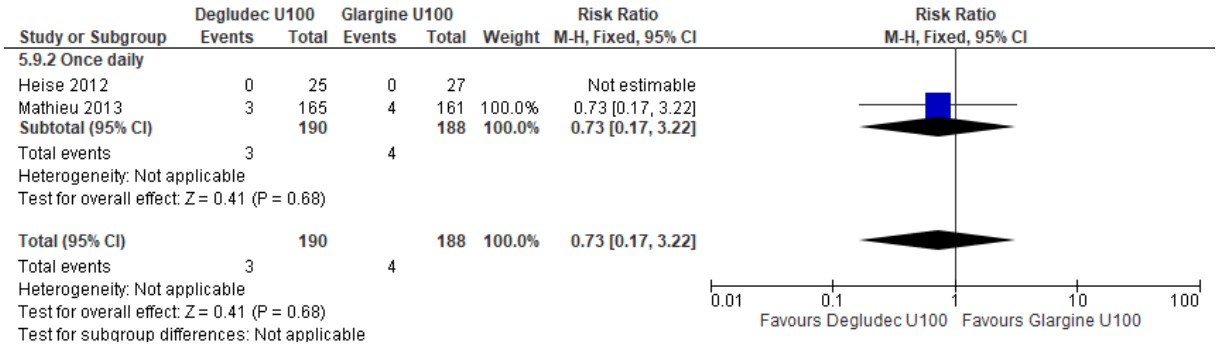
(MD less than 0 favours once daily degludec U100)



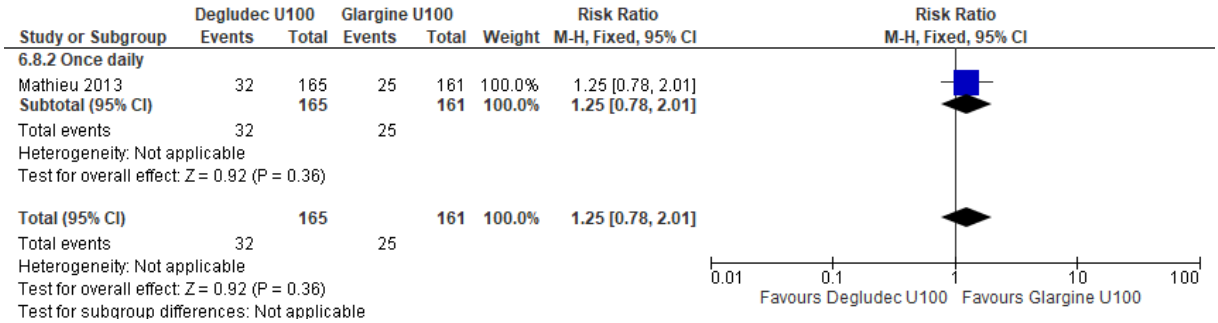
Footnotes

(1) Data taken from period 1 (16 weeks)

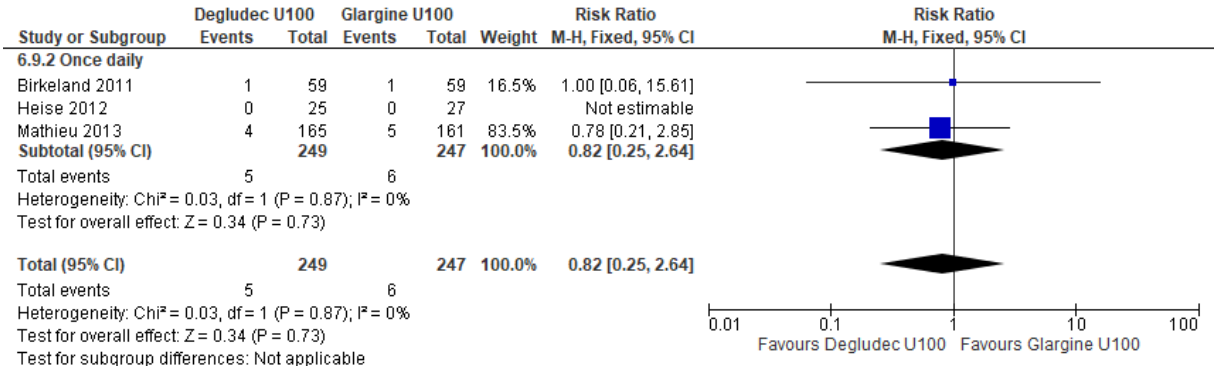
Injection site reactions



Adverse events

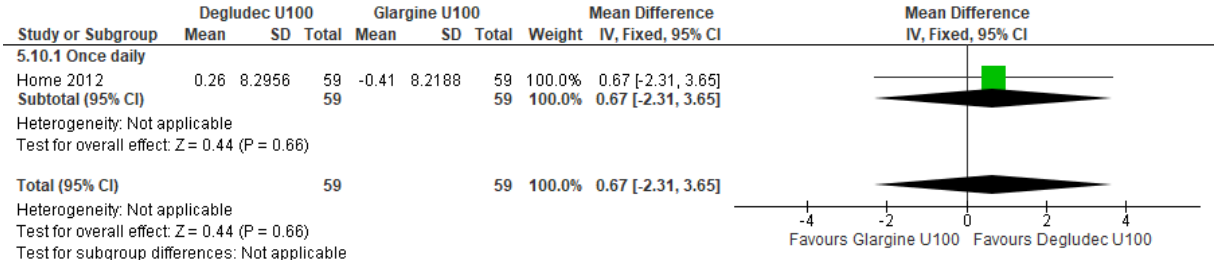


Serious AEs



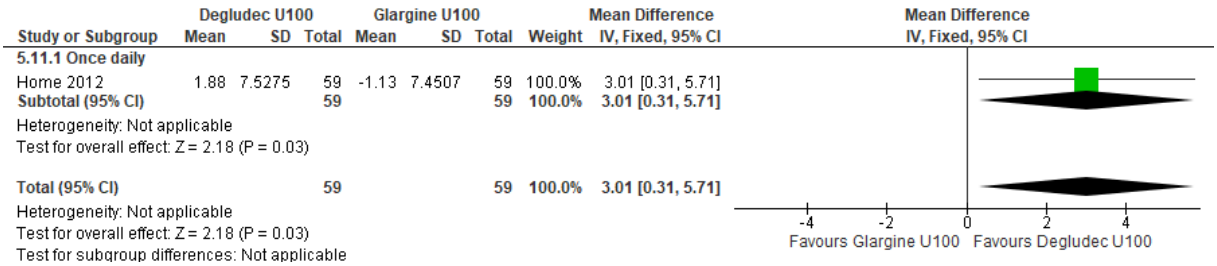
Quality of life – Change in SF36 physical component scores (higher score= better outcome)

(MD greater than 0 favours degludec U100)



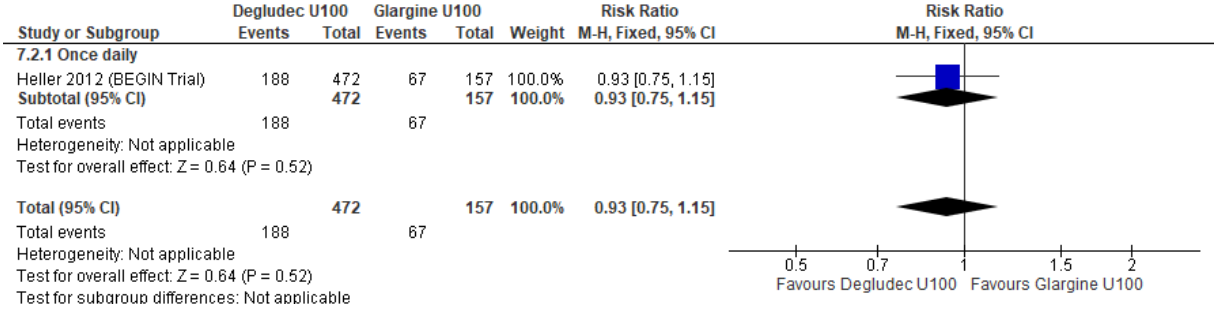
Quality of life – Change in SF36 mental component scores (higher score= better outcome)

(MD greater than 0 favours degludec U100)



Outcomes > 6 months

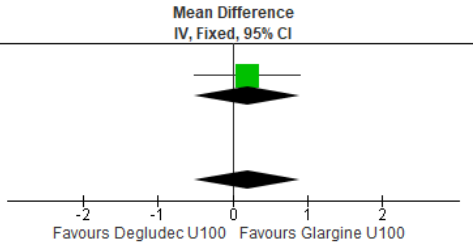
Patients achieving HbA1c target (<7%, <53mmol/mol)



Change in weight (kg)

(MD less than 0 favours once daily degludec U100)

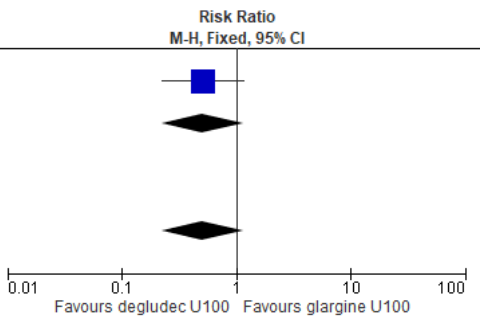
Study or Subgroup	Degludec U100 Mean	SD	Total	Glargine U100 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.6.1 Once daily								
Heller 2012 (BEGIN Trial)	1.8	4.3451	472	1.6	3.759	157	100.0%	0.20 [-0.51, 0.91]
Subtotal (95% CI)			**472**			**157**	**100.0%**	**0.20 [-0.51, 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								
Total (95% CI)			**472**			**157**	**100.0%**	**0.20 [-0.51, 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								
Test for subgroup differences: Not applicable								



Injection site reaction

Study or Subgroup	Degludec U100 Events	Total	Glargine U100 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.7.1 Once daily						
Bode 2013 (BEGIN trial) (1)	14	472	9	154	100.0%	0.51 [0.22, 1.15]
Heller 2012 (BEGIN Trial) (2)	13	472	8	154		Not estimable
Subtotal (95% CI)		**472**		**154**	**100.0%**	**0.51 [0.22, 1.15]**
Total events	14		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
Total (95% CI)		**472**		**154**	**100.0%**	**0.51 [0.22, 1.15]**
Total events	14		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Not applicable						

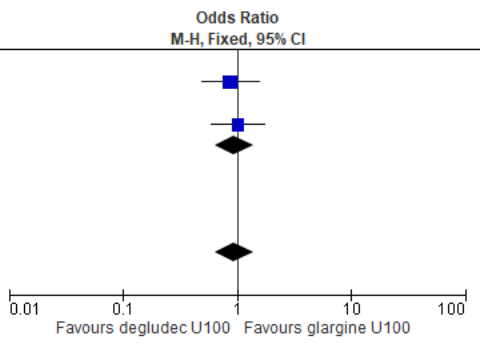
Footnotes
(1) 104 weeks follow up of BEGIN trial
(2) 52 weeks follow up af BEGIN trial. Data from longest followup time included.



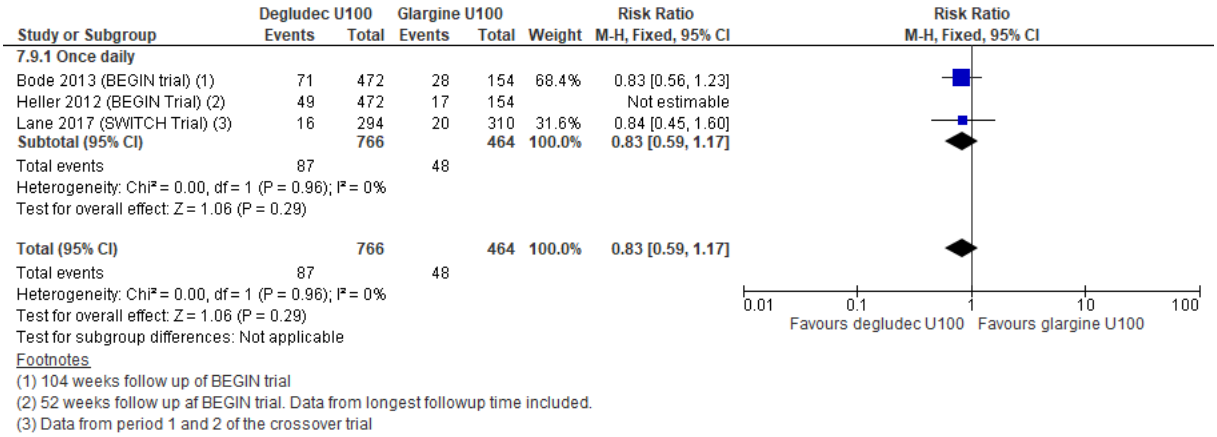
Adverse events

Study or Subgroup	Degludec U100 Events	Total	Glargine U100 Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
7.8.1 Once daily						
Bode 2013 (BEGIN trial) (1)	413	472	137	154	50.3%	0.87 [0.49, 1.54]
Heller 2012 (BEGIN Trial) (2)	102	472	26	154		Not estimable
Lane 2017 (SWITCH Trial) (3)	28	294	29	310	49.7%	1.02 [0.59, 1.76]
Subtotal (95% CI)		**766**		**464**	**100.0%**	**0.94 [0.64, 1.40]**
Total events	441		166			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**766**		**464**	**100.0%**	**0.94 [0.64, 1.40]**
Total events	441		166			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Not applicable						

Footnotes
(1) 104 weeks follow up of BEGIN trial
(2) 52 weeks follow up af BEGIN trial. Data from longest followup time included.
(3) Data from period 1 and 2 of the crossover trial



Serious AEs



Footnotes

(1) 104 weeks follow up of BEGIN trial

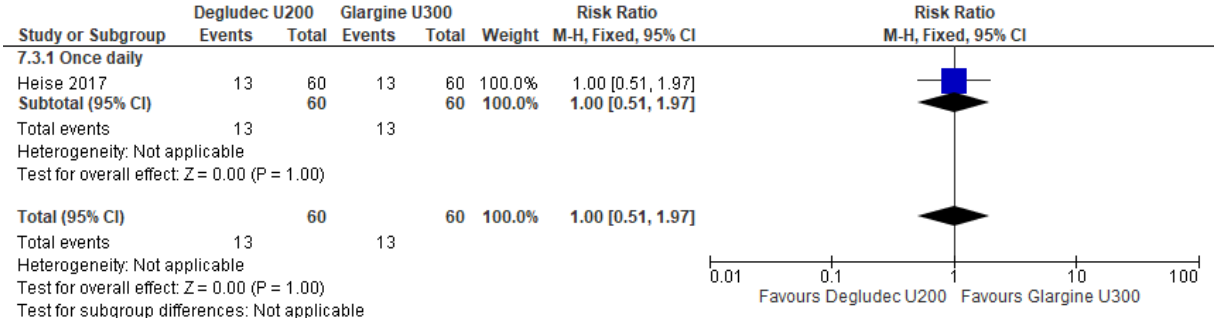
(2) 52 weeks follow up af BEGIN trial. Data from longest followup time included.

(3) Data from period 1 and 2 of the crossover trial

Degludec U200 vs Glargine U300

Outcomes ≤ 6 months

Adverse events

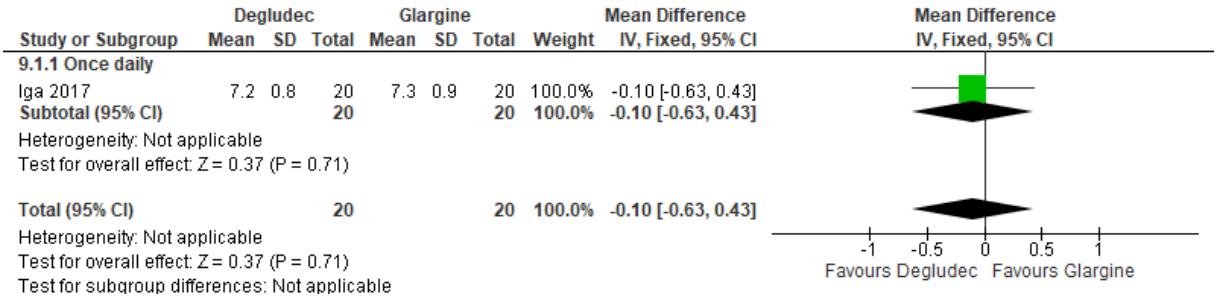


Degludec vs Glargine (conc. Unknown)

Outcomes ≤ 6 months

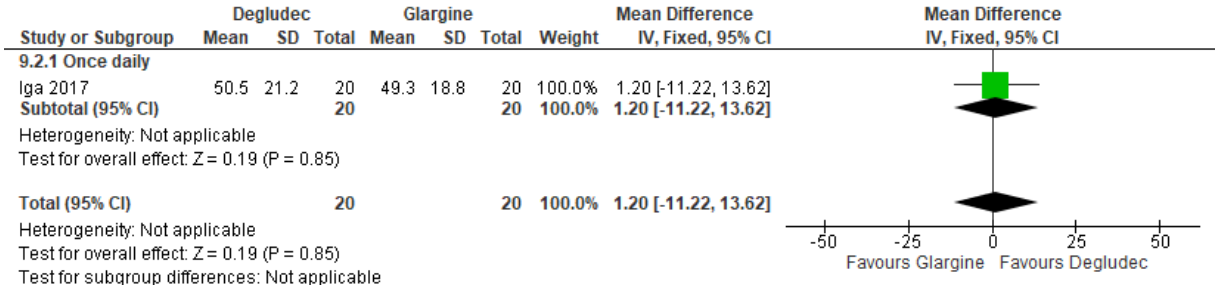
HbA1c (%) at follow up

(MD less than 0 favours once daily degludec)



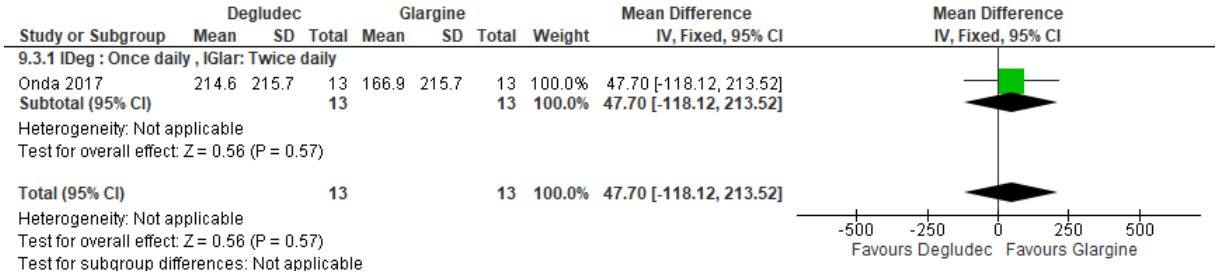
Percentage of time in target glucose range (70 and 140 mg/dL (3.9–7.8 mmol/L))

(MD greater than 0 favours once daily degludec)



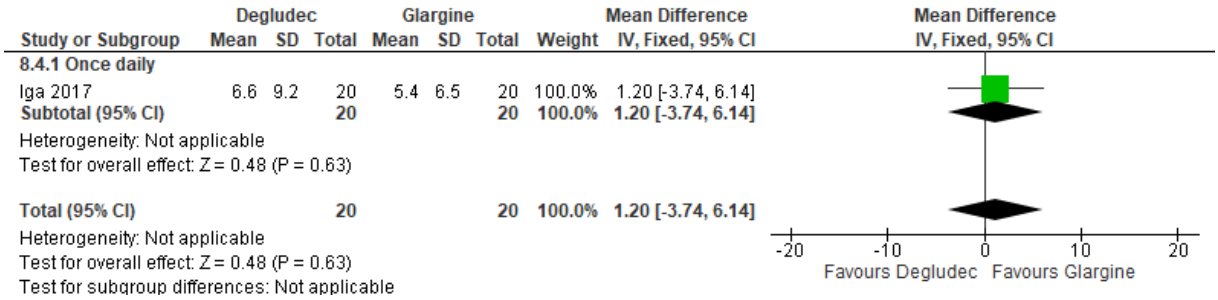
Time in hypoglycaemia (<70 mg/dL) during 24h (mins)

(MD less than 0 favours once daily degludec)



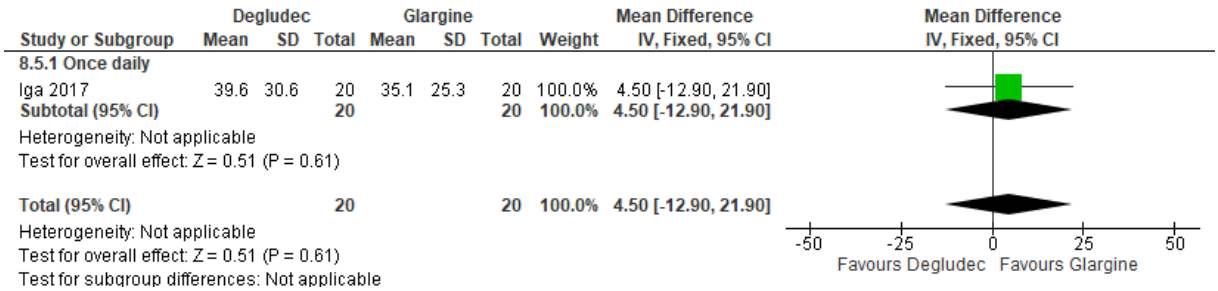
Percentage of time in hypoglycaemia

(MD greater than 0 favours once daily degludec)



Percentage time in nocturnal hypoglycaemia

(MD less than 0 favours once daily degludec)

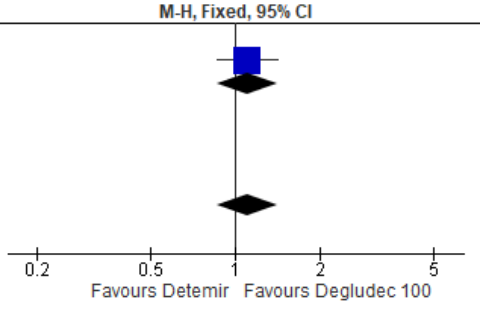


Degludec U100 vs Detemir

Outcomes ≤ 6 months

Participants achieving HbA1c <7%

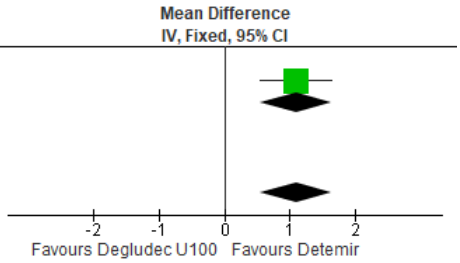
Study or Subgroup	Degludec U100 Events	Total	Detemir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.3.1 Once daily						
Davies 2014	124	302	57	153	100.0%	1.10 [0.86, 1.41]
Subtotal (95% CI)		**302**		**153**	**100.0%**	**1.10 [0.86, 1.41]**
Total events	124		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)		**302**		**153**	**100.0%**	**1.10 [0.86, 1.41]**
Total events	124		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Not applicable						



Change in weight (kg)

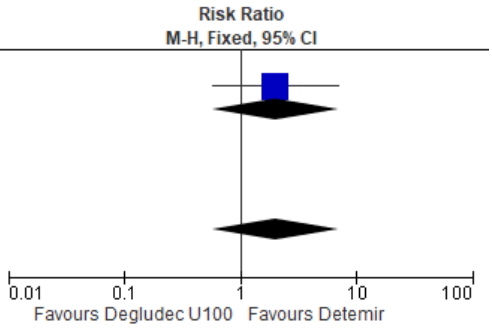
(MD less than 0 favours once daily degludec U100)

Study or Subgroup	Degludec U100 Mean	SD	Total	Detemir Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
13.7.1 Once daily								
Davies 2014	1.5	2.8496	203	0.4	2.4739	153	100.0%	1.10 [0.55, 1.65]
Subtotal (95% CI)			**203**			**153**	**100.0%**	**1.10 [0.55, 1.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.89 (P = 0.0001)								
Total (95% CI)			**203**			**153**	**100.0%**	**1.10 [0.55, 1.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.89 (P = 0.0001)								
Test for subgroup differences: Not applicable								

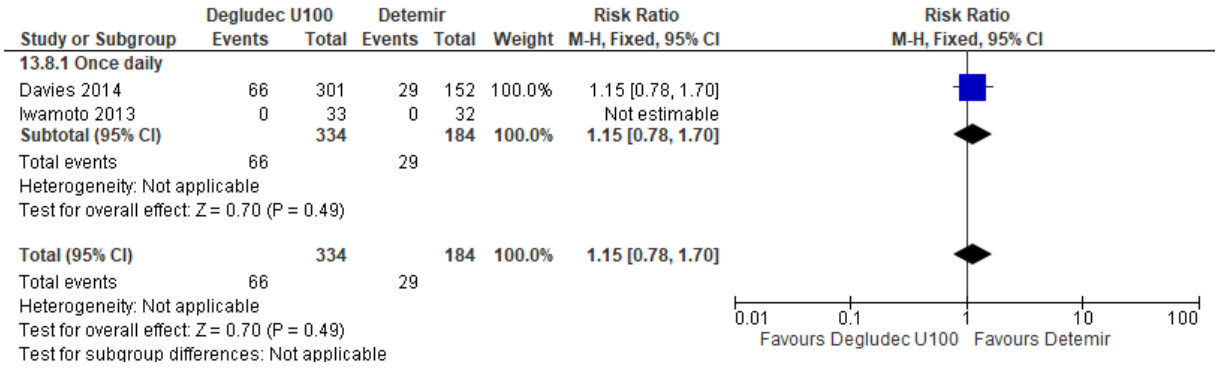


Injection site reactions

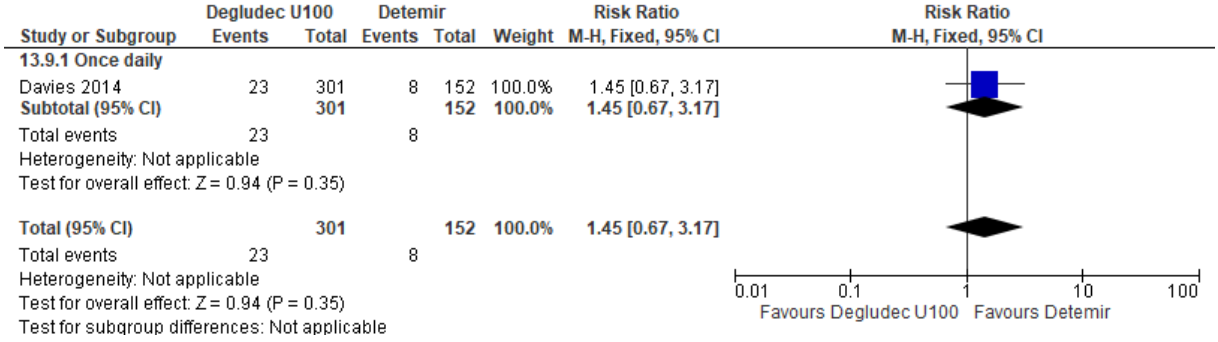
Study or Subgroup	Degludec U100 Events	Total	Detemir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.10.1 Once daily						
Davies 2014	12	301	3	152	100.0%	2.02 [0.58, 7.05]
Subtotal (95% CI)		**301**		**152**	**100.0%**	**2.02 [0.58, 7.05]**
Total events	12		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Total (95% CI)		**301**		**152**	**100.0%**	**2.02 [0.58, 7.05]**
Total events	12		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Not applicable						



Adverse events



Serious AEs

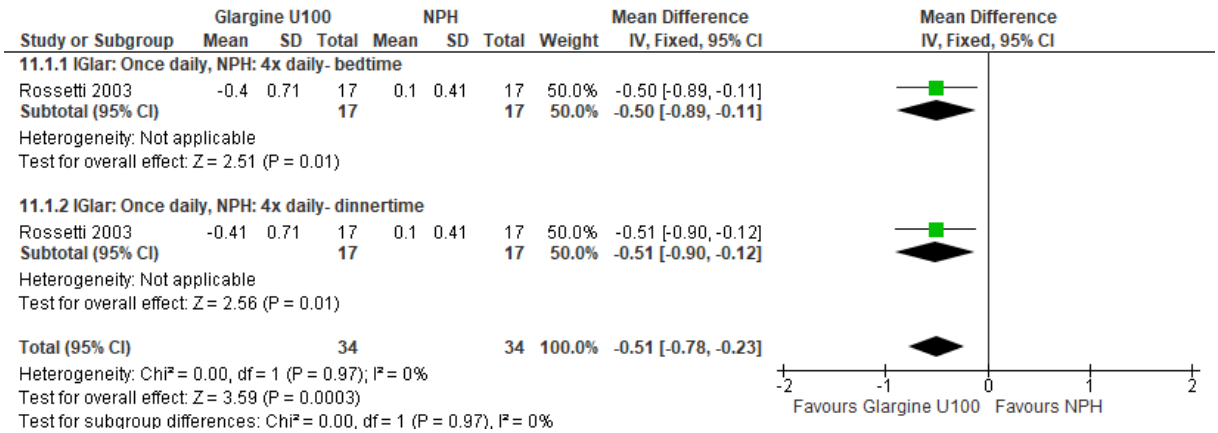


Glargine U100 vs NPH

Outcomes ≤ 6 months

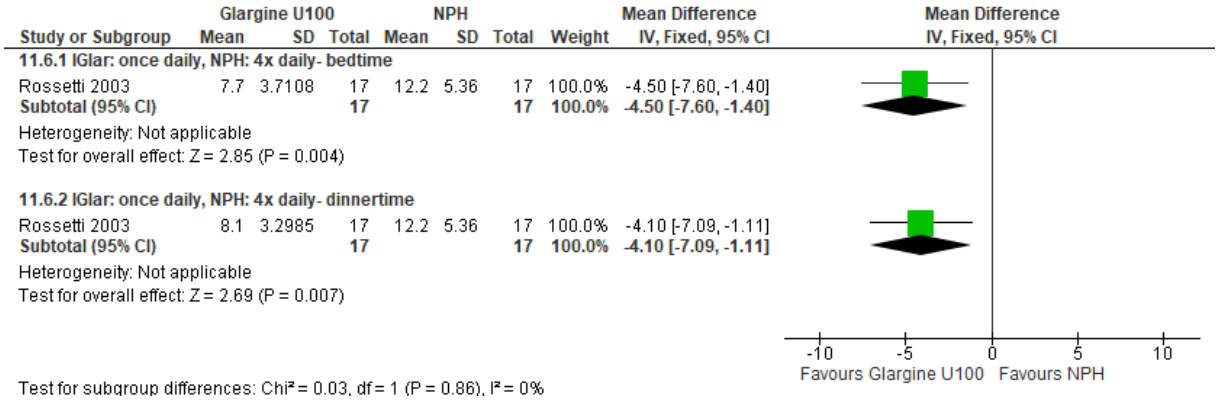
Change in HbA1c (%)

(MD less than 0 favours once daily glargine U100)



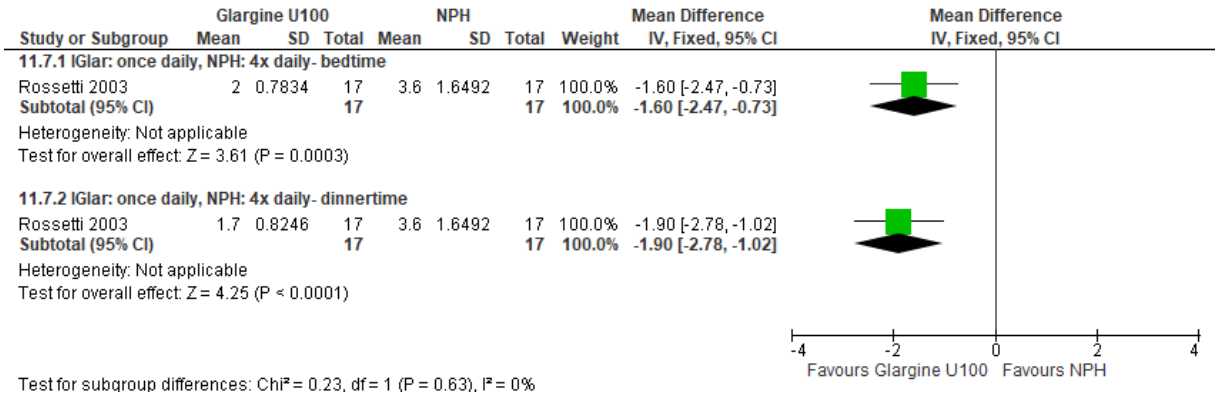
Frequency of mild hypoglycaemia (episodes/ patient/ month)

(MD less than 0 favours once daily glargine U100)



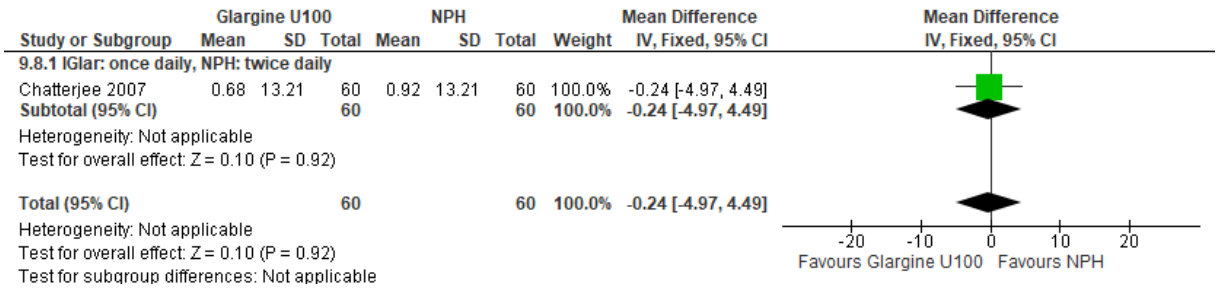
Frequency of nocturnal hypoglycaemia (episodes/ patient/ month)

(MD less than 0 favours once daily glargine U100)



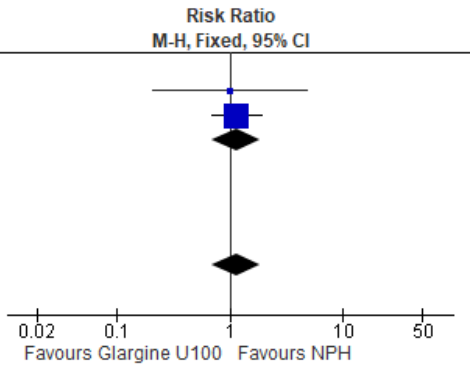
Change in weight (kg)

(MD less than 0 favours once daily glargine U100)



Injection site reactions

Study or Subgroup	Glargine U100 Events	Total	NPH Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.9.1 IGlar:Once daily, NPH once or twice						
Pieber 2000 (1)	3	110	3	110	10.7%	1.00 [0.21, 4.85]
Raskin 2000	36	310	21	209	89.3%	1.16 [0.69, 1.92]
Subtotal (95% CI)		**420**		**319**	**100.0%**	**1.14 [0.70, 1.85]**
Total events	39		24			
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Total (95% CI)		**420**		**319**	**100.0%**	**1.14 [0.70, 1.85]**
Total events	39		24			
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Test for subgroup differences: Not applicable						

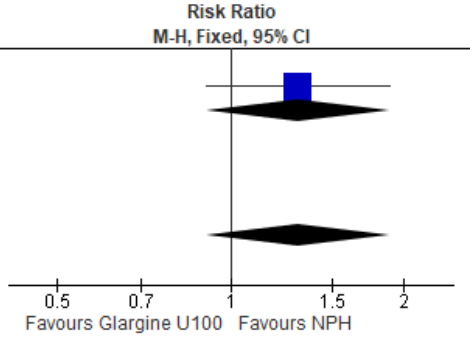


Footnotes

(1) IGlar U100 including 30 µg/ml zinc

Adverse events

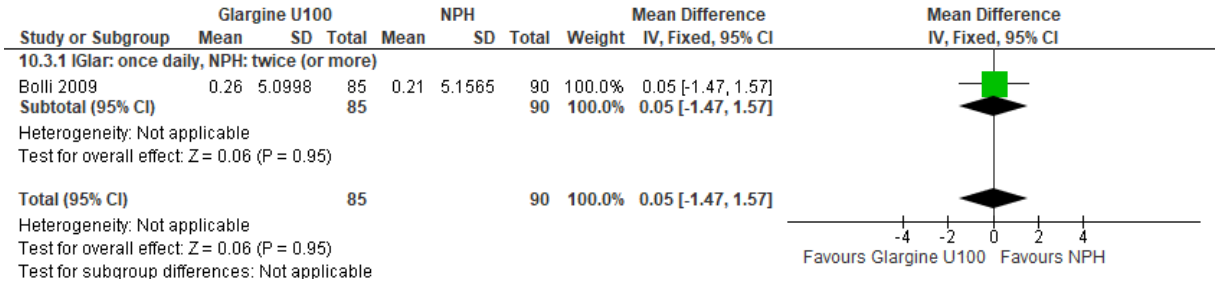
Study or Subgroup	Glargine U100 Events	Total	NPH Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.10.1 IGlar:Once daily, NPH once or twice						
Raskin 2000	68	310	35	209	100.0%	1.31 [0.91, 1.89]
Subtotal (95% CI)		**310**		**209**	**100.0%**	**1.31 [0.91, 1.89]**
Total events	68		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
Total (95% CI)		**310**		**209**	**100.0%**	**1.31 [0.91, 1.89]**
Total events	68		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
Test for subgroup differences: Not applicable						



Outcomes > 6 months

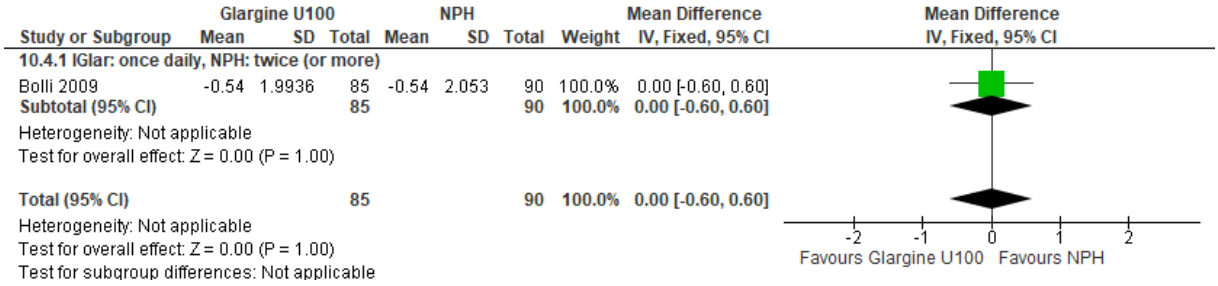
Change in hypoglycaemia (episodes/ patient/ month)

(MD less than 0 favours once daily glargine U100)



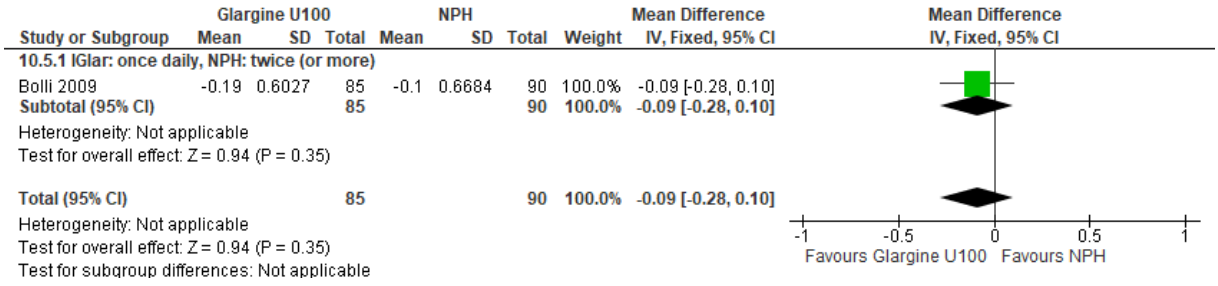
Change in severe hypoglycaemia (episodes/ patient/ month)

(MD less than 0 favours once daily glargine U100)



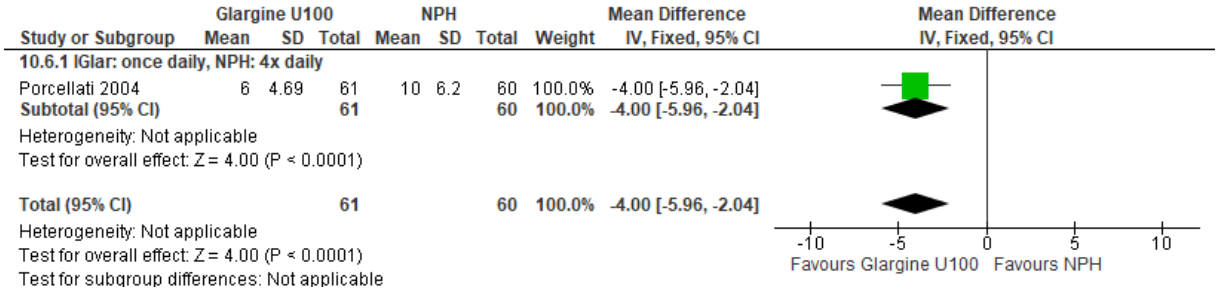
Change in severe nocturnal hypoglycaemia (episodes/ patient/ month)

(MD less than 0 favours once daily glargine U100)



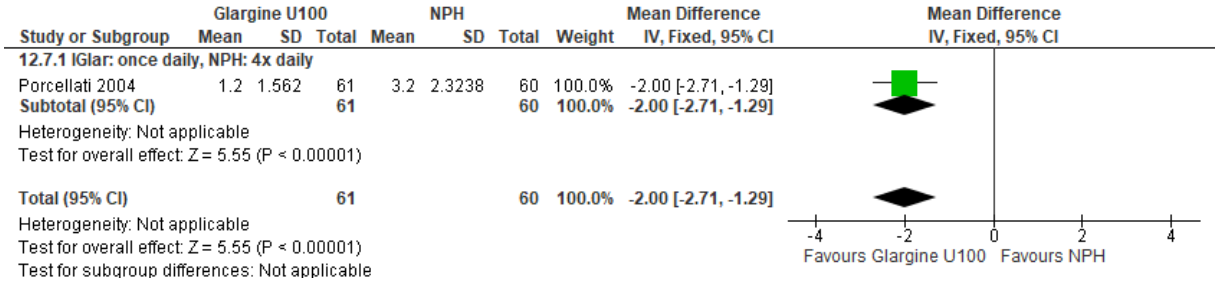
Frequency of hypoglycaemia (episodes/ patient/ month)

(MD less than 0 favours once daily glargine U100)

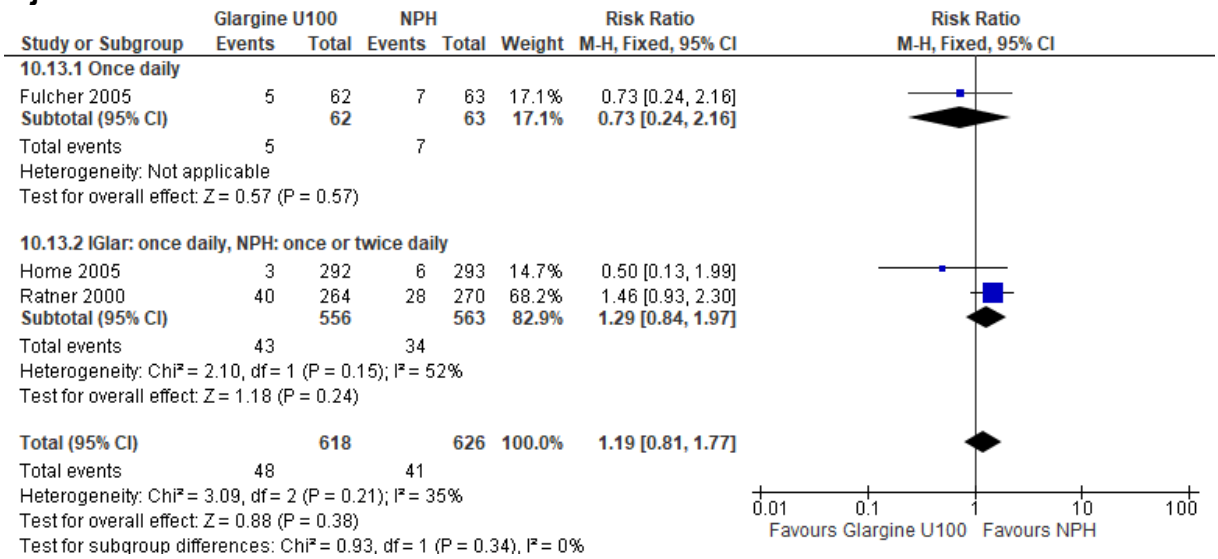


Frequency of nocturnal hypoglycaemia (episodes/ patient/ month)

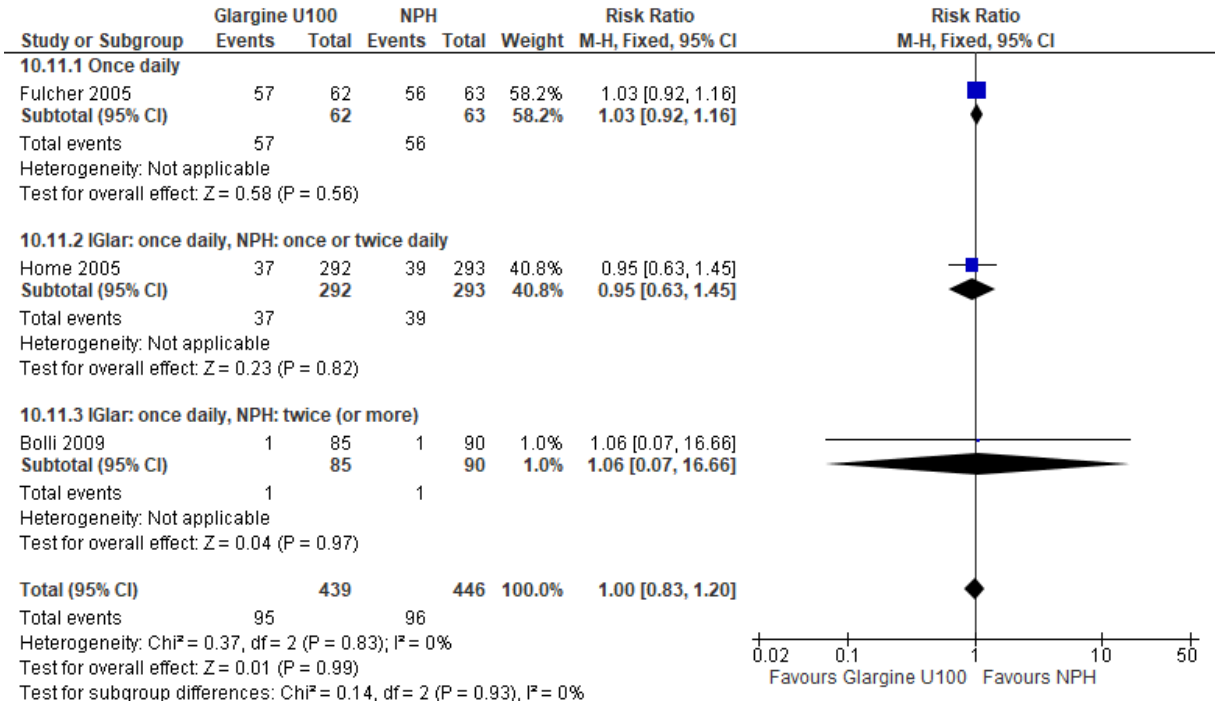
(MD less than 0 favours once daily glargine U100)



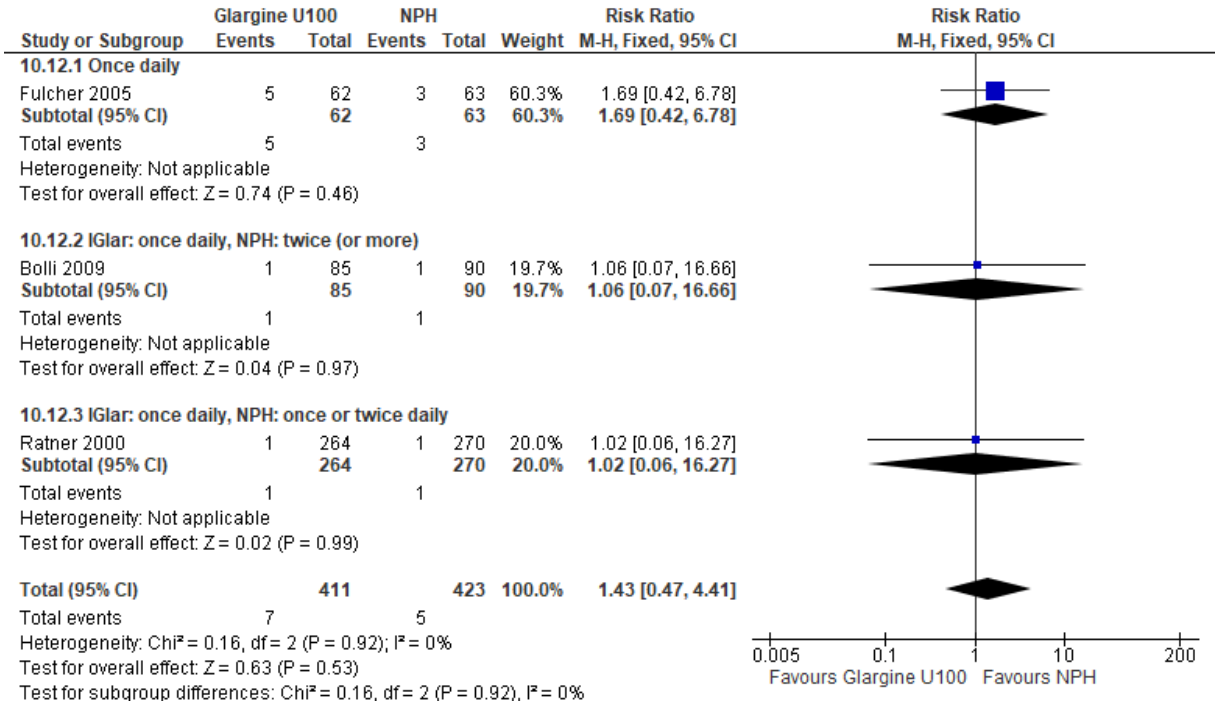
Injection site reactions



Adverse events

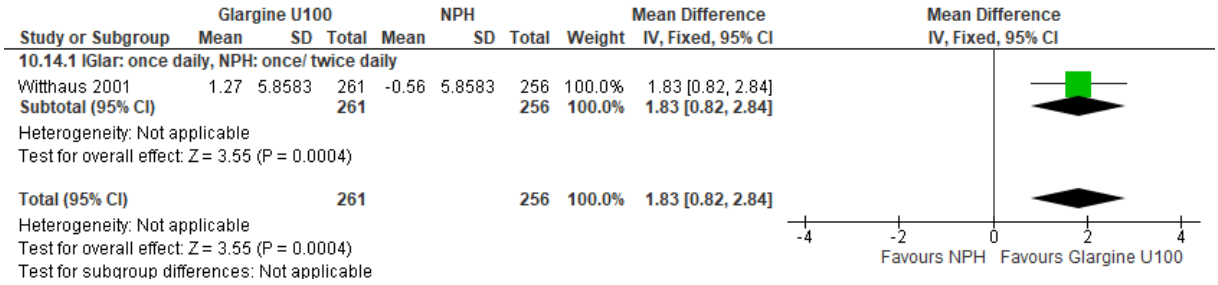


Serious AEs



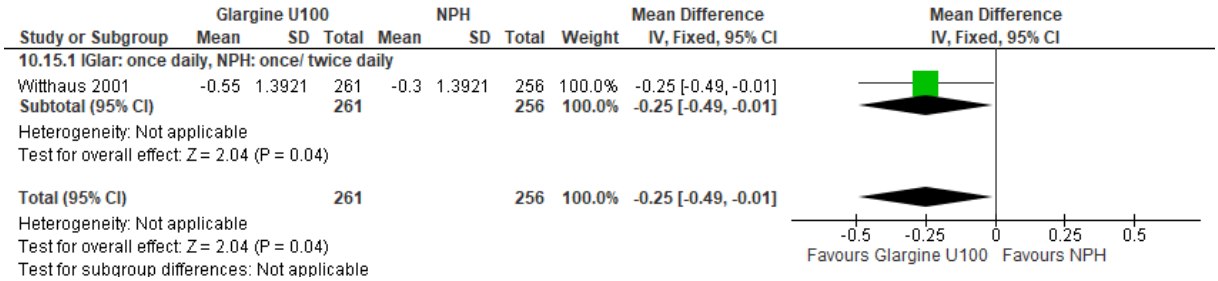
QoL – DTSQ- change in treatment satisfaction from baseline

(higher score indicating greater satisfaction)



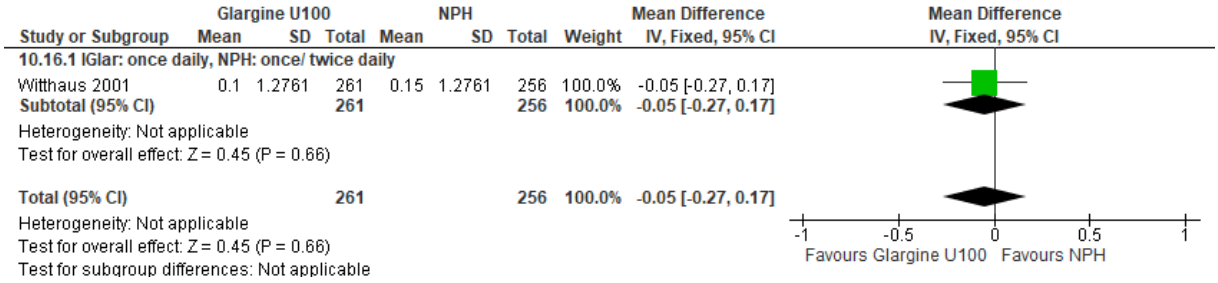
QoL – DTSQ- change in perceived frequency of hyperglycaemia from baseline

(Lower score indicates greater satisfaction)



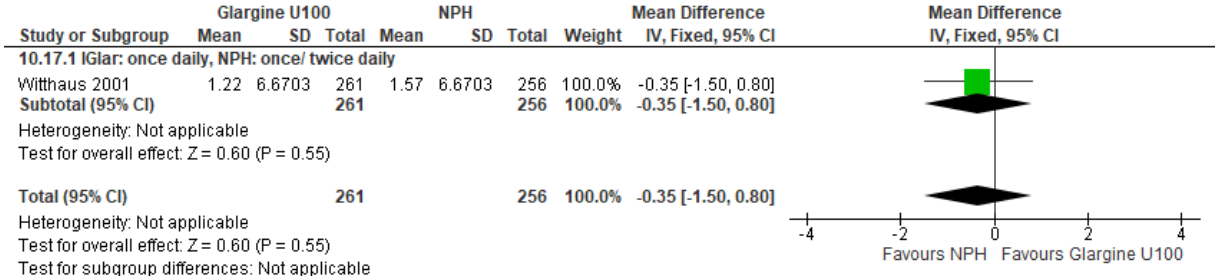
QoL – DTSQ- change in perceived frequency of hypoglycaemia from baseline

(Lower score indicates greater satisfaction)



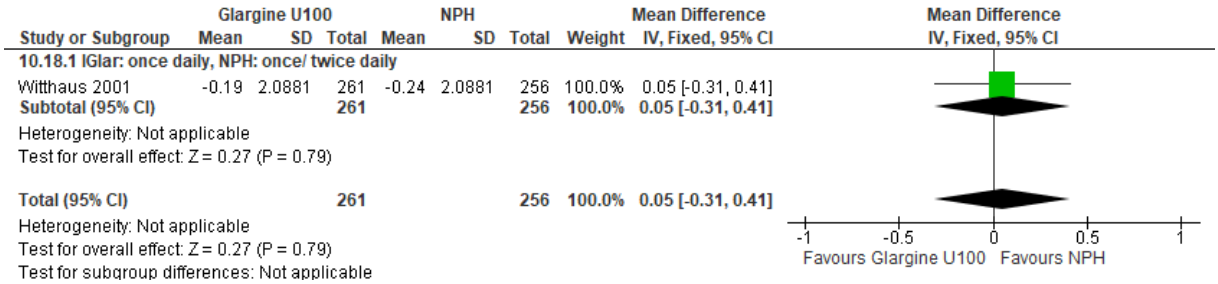
QoL – W-BQ22- change in general wellbeing from baseline

(Higher score indicates greater wellbeing)



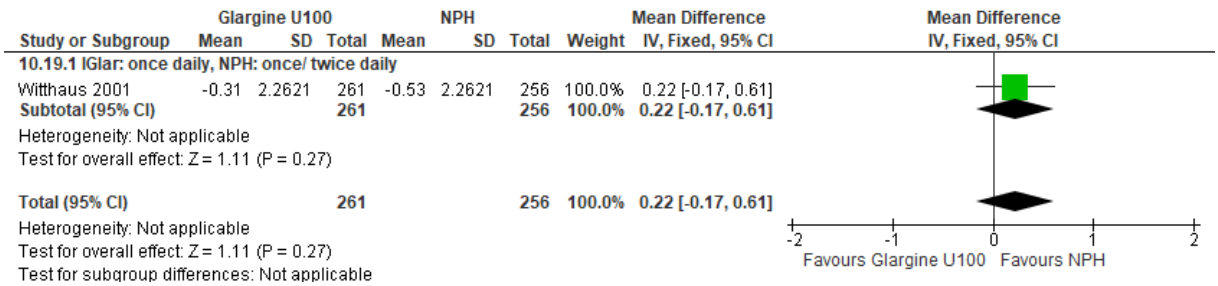
QoL – W-BQ22- change in depression from baseline

(Lower score indicates greater wellbeing)



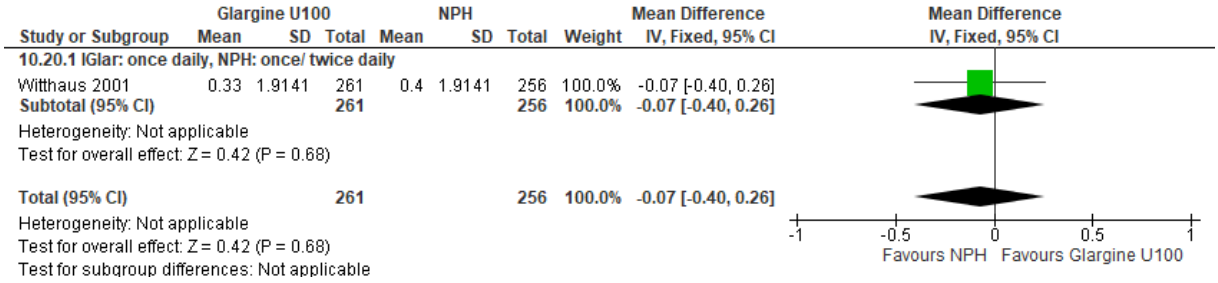
QoL – W-BQ22- change in anxiety from baseline

(Lower score indicates greater wellbeing)



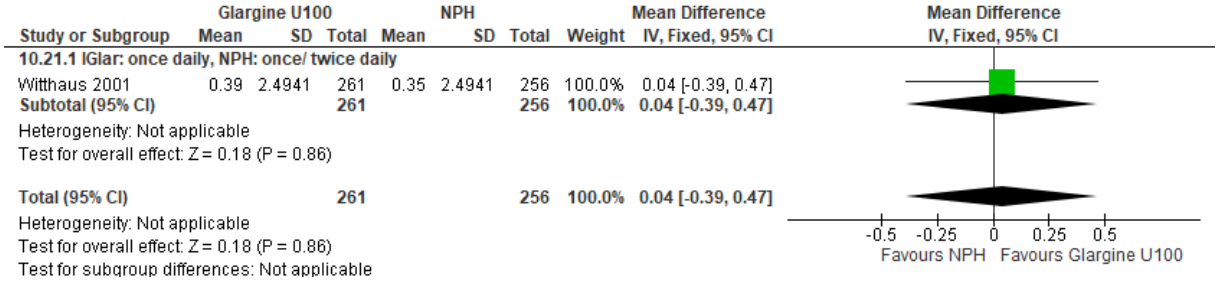
QoL – W-BQ22- change in energy from baseline

(Higher score indicates greater wellbeing)



QoL – W-BQ22- change in positive wellbeing from baseline

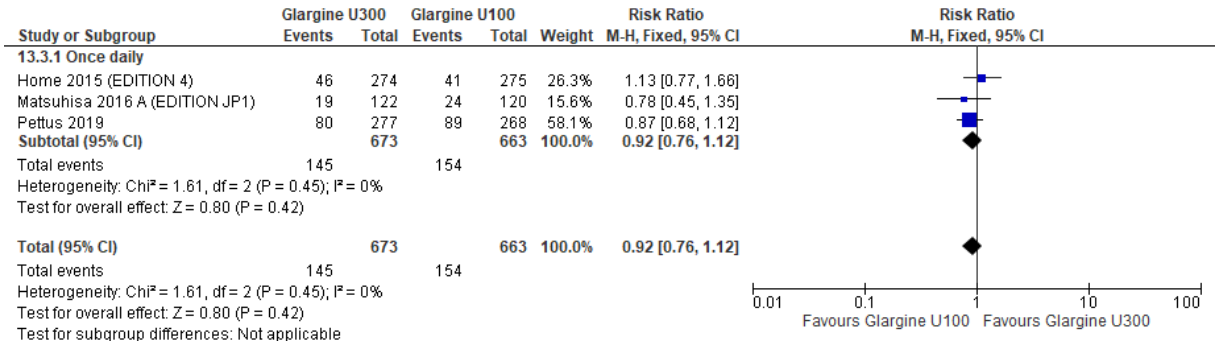
(Higher score indicates greater wellbeing)



Glargine U300 vs Glargine U100

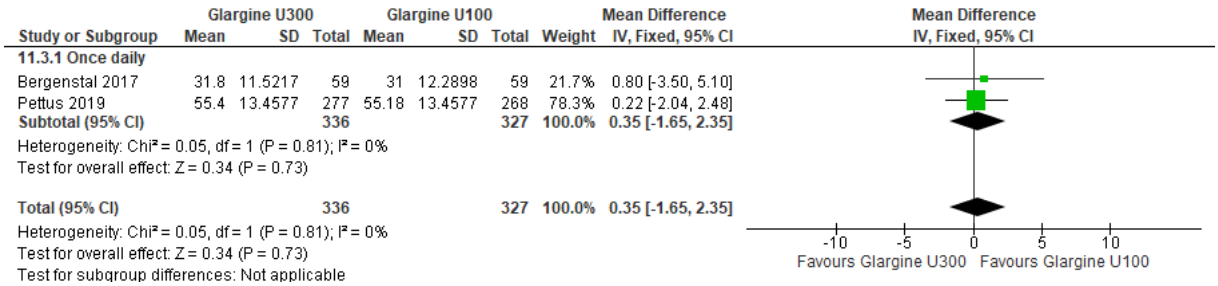
Outcomes ≤ 6 months

Patients achieving HbA1c <7%



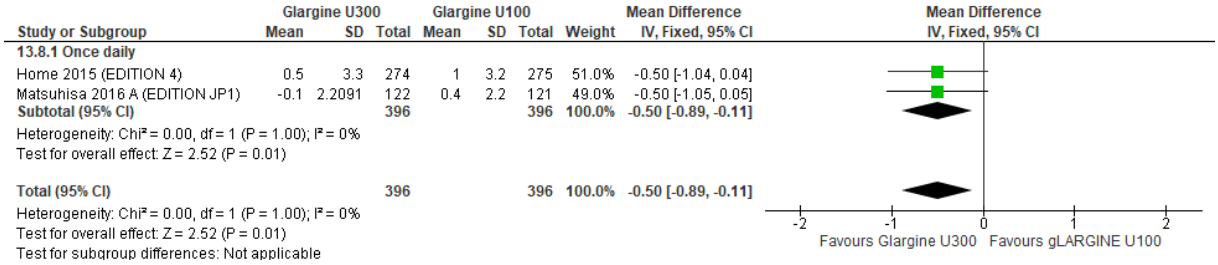
Percentage of time spent in target glucose range

(MD greater than 0 favours once daily glargine U300)

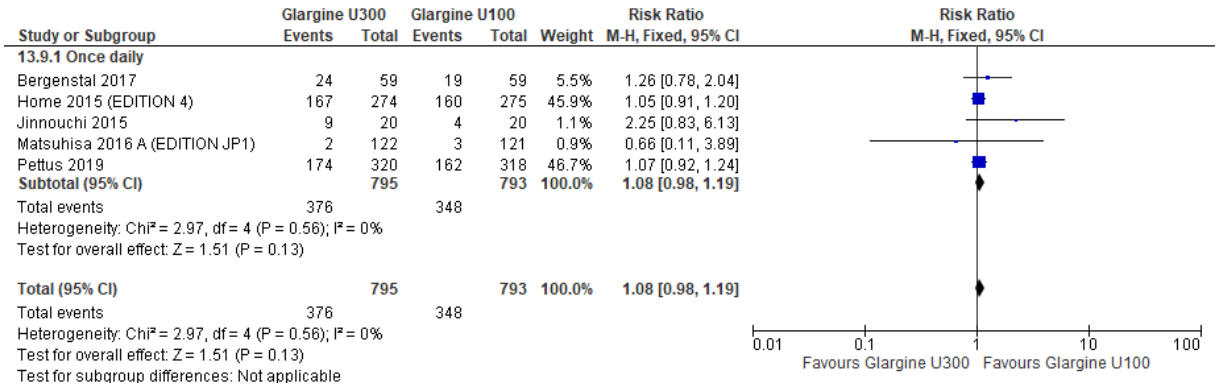


Change in weight (kg)

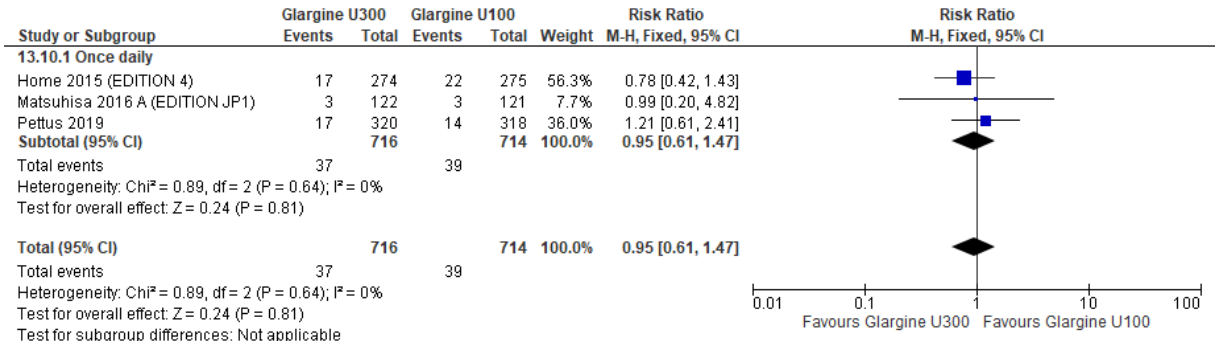
(MD less than 0 favours once daily glargine U300)



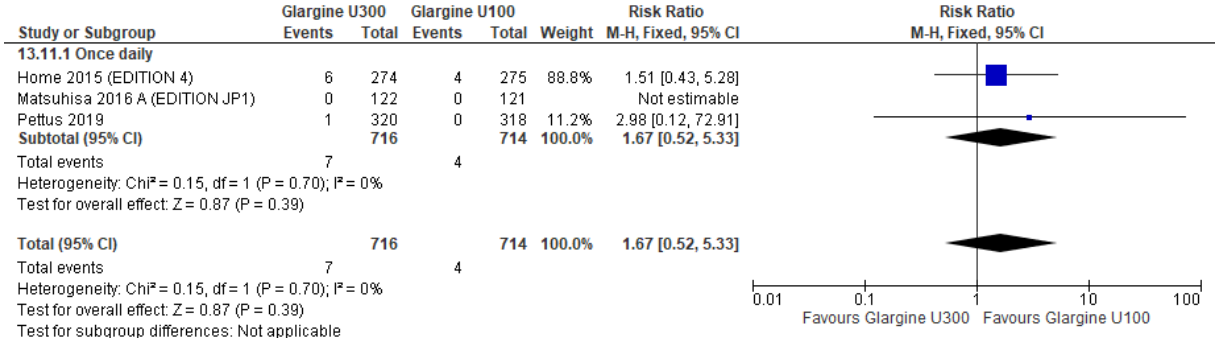
Adverse events



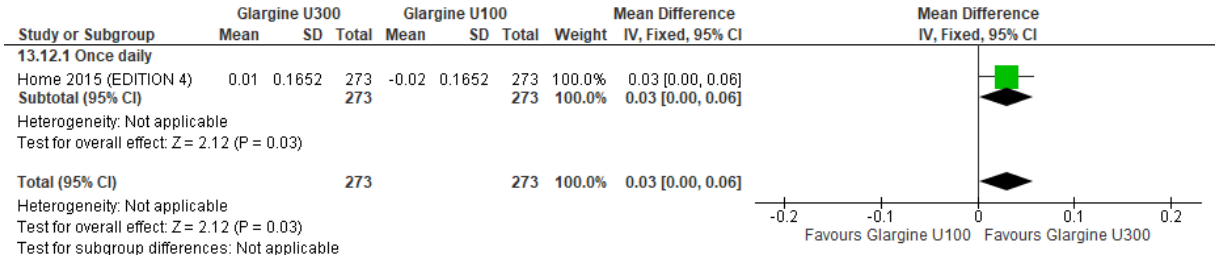
Serious AEs



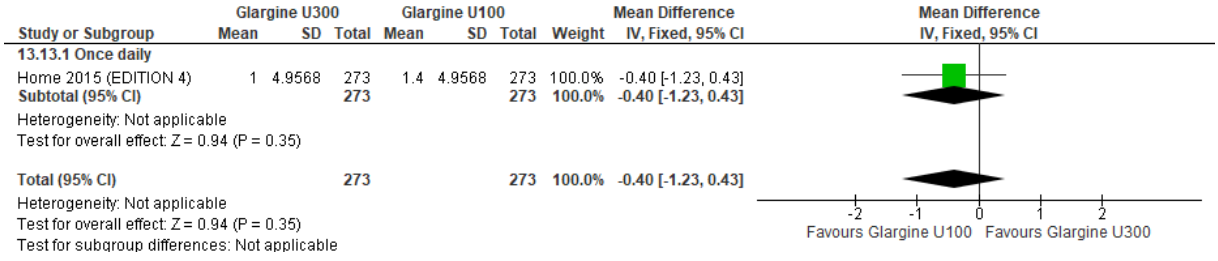
Injection site reactions



QoL- Change in EQ-5D utility index (Higher score indicates better QoL)



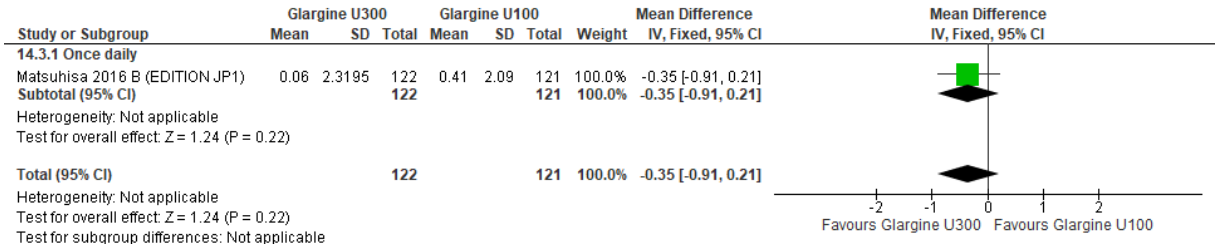
QoL- Change in DTSQ (Higher score indicates better satisfaction)



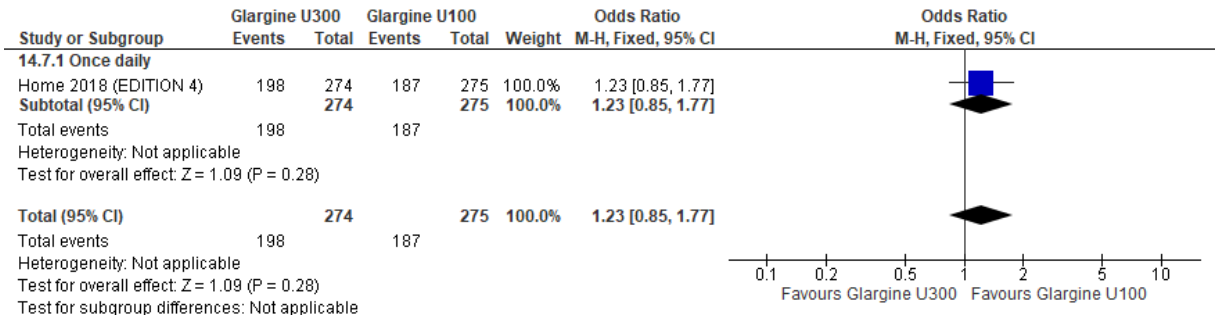
Outcomes > 6 months

Change in weight (kg)

(MD less than 0 favours once daily glargine U300)

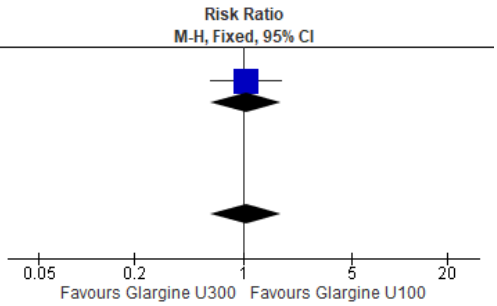


Adverse events



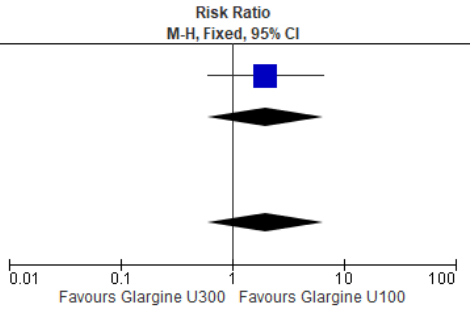
Serious AEs

Study or Subgroup	Glargine U300 Events	Total	Glargine U100 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.9.1 Once daily						
Home 2018 (EDITION 4)	27	274	26	275	100.0%	1.04 [0.62, 1.74]
Subtotal (95% CI)		**274**		**275**	**100.0%**	**1.04 [0.62, 1.74]**
Total events	27		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
Total (95% CI)		**274**		**275**	**100.0%**	**1.04 [0.62, 1.74]**
Total events	27		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Not applicable						



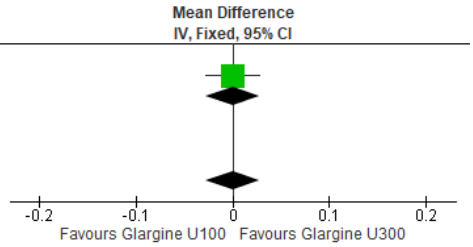
Injection site reactions

Study or Subgroup	Glargine U300 Events	Total	Glargine U100 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.10.1 Once daily						
Home 2018 (EDITION 4)	8	274	4	275	100.0%	2.01 [0.61, 6.59]
Matsuhisa 2016 B (EDITION JP1)	0	122	0	121		Not estimable
Subtotal (95% CI)		**396**		**396**	**100.0%**	**2.01 [0.61, 6.59]**
Total events	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)		**396**		**396**	**100.0%**	**2.01 [0.61, 6.59]**
Total events	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Not applicable						



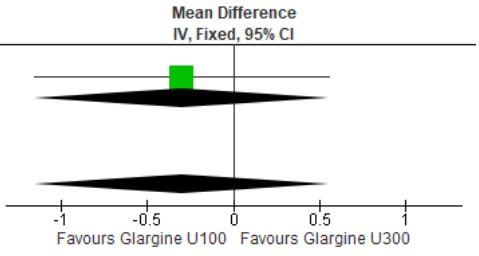
QoL- Change in EQ-5D utility index (Higher score indicates better QoL)

Study or Subgroup	Glargine U300 Mean	SD	Total	Glargine U100 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
14.11.1 Once daily								
Home 2018 (EDITION 4)	0	0.1652	273	0	0.1652	273	100.0%	0.00 [-0.03, 0.03]
Subtotal (95% CI)			**273**			**273**	**100.0%**	**0.00 [-0.03, 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**273**			**273**	**100.0%**	**0.00 [-0.03, 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								

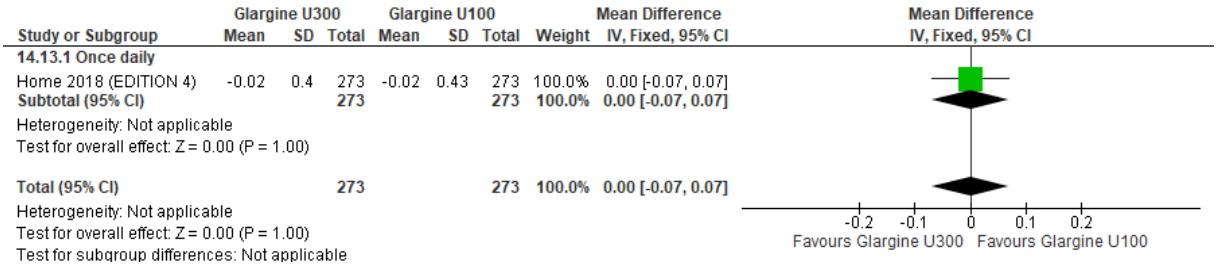


QoL- Change in DTSQ (Higher score indicates better satisfaction)

Study or Subgroup	Glargine U300 Mean	SD	Total	Glargine U100 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
14.12.1 Once daily								
Home 2018 (EDITION 4)	1.3	5.3	273	1.6	4.9	273	100.0%	-0.30 [-1.16, 0.56]
Subtotal (95% CI)			**273**			**273**	**100.0%**	**-0.30 [-1.16, 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
Total (95% CI)			**273**			**273**	**100.0%**	**-0.30 [-1.16, 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
Test for subgroup differences: Not applicable								



QoL- Change in HFSII score (lower score indicating less fear of hypoglycaemia)

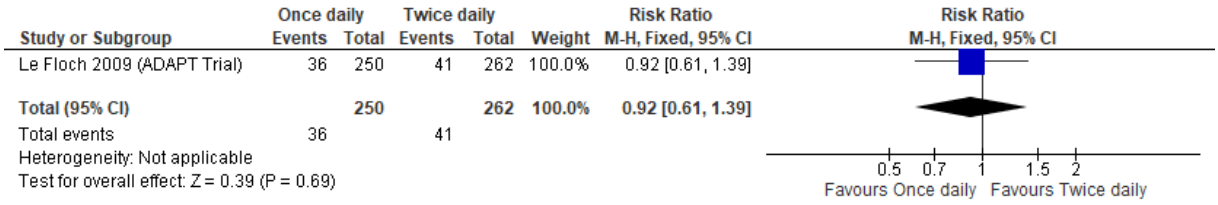


Frequency of administration

Detemir once daily vs detemir twice daily

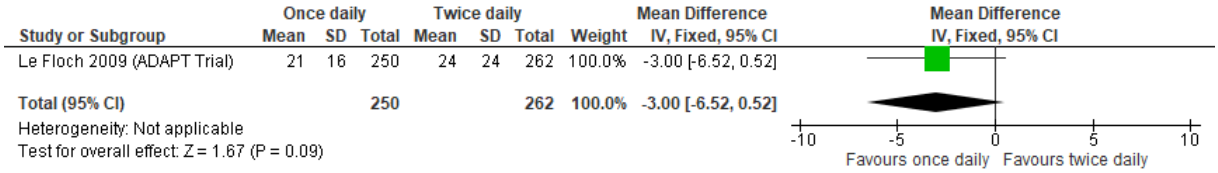
Outcomes ≤ 6 months

Participants achieving HbA1c <7%



Frequency of hypoglycaemia (events/ patient/ 14 days)

(MD less than 0 favours once daily detemir)



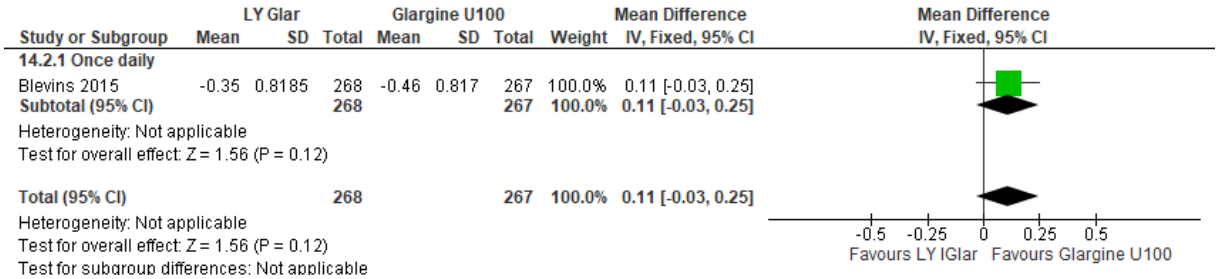
Biosimilars

LY IGlar vs Glargine U100

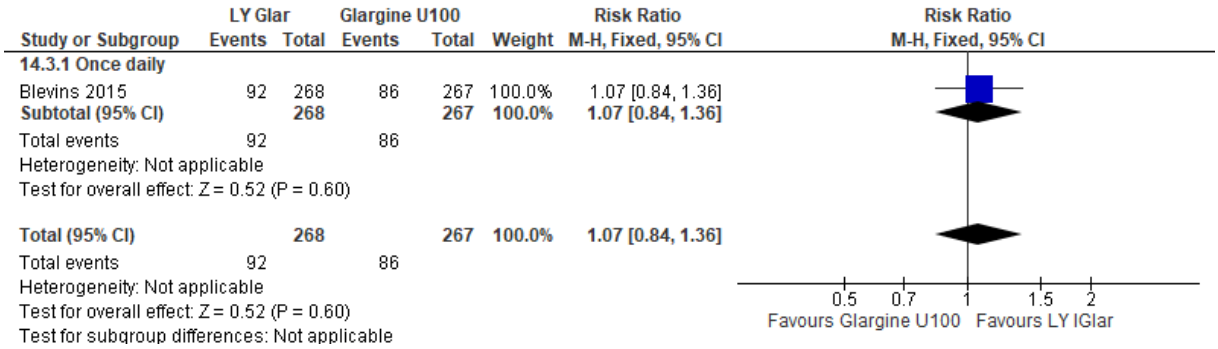
Outcomes ≤ 6 months

Change in HbA1c (%)

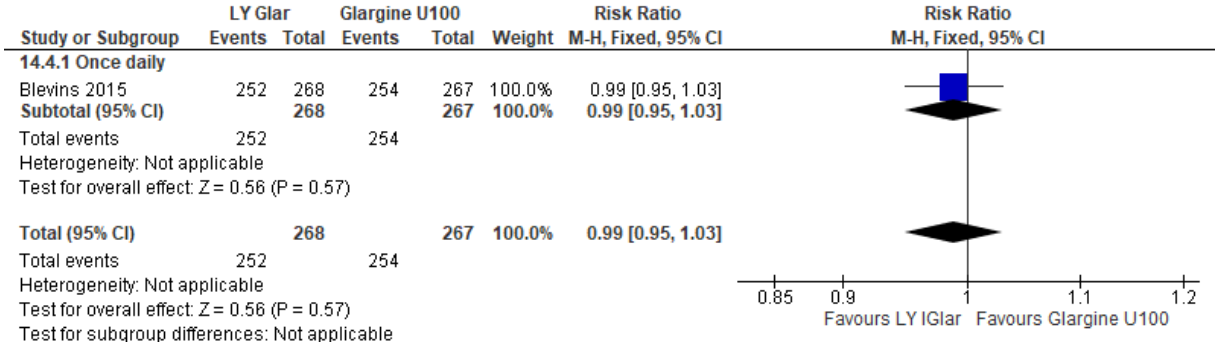
(MD less than 0 favours once daily LY IGlar)



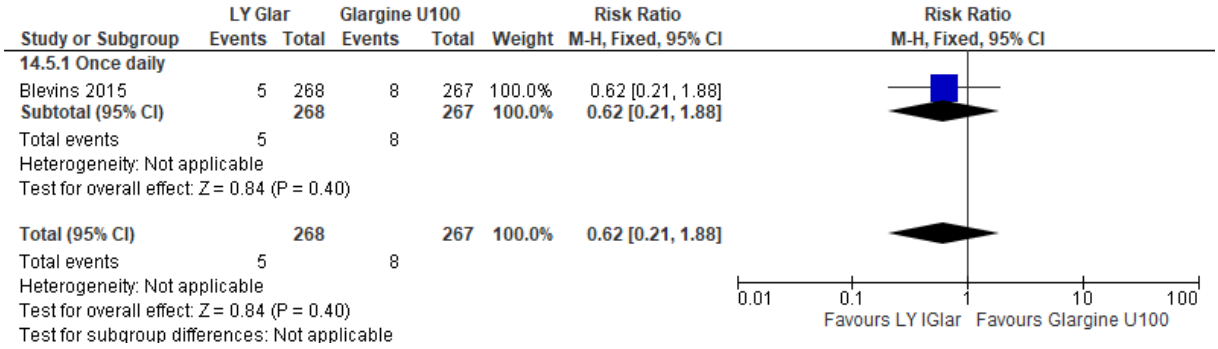
Participants achieving HbA1c <7%



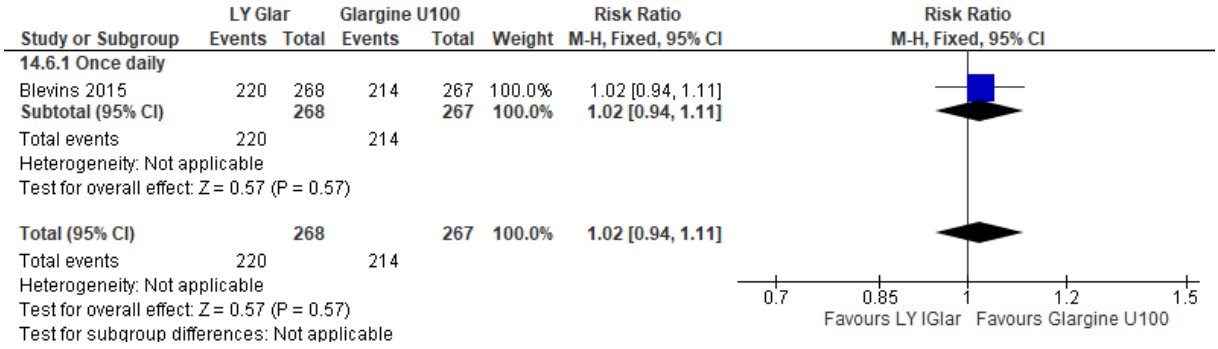
Hypoglycaemia (all)



Major/ severe hypoglycaemia

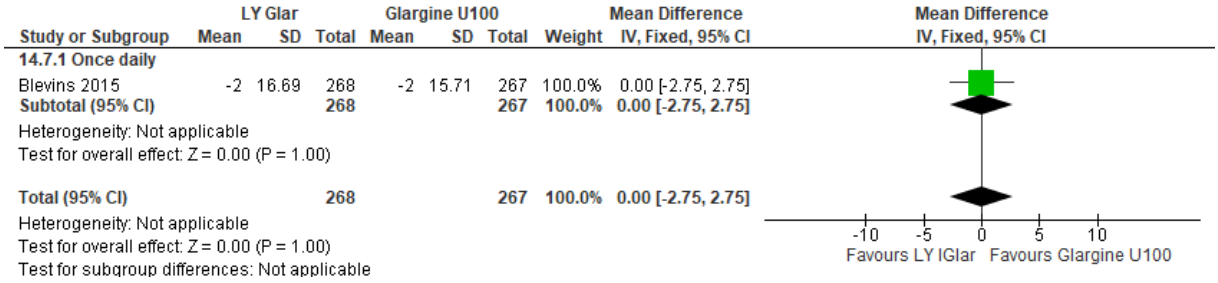


Nocturnal hypoglycaemia



Change in weight (kg)

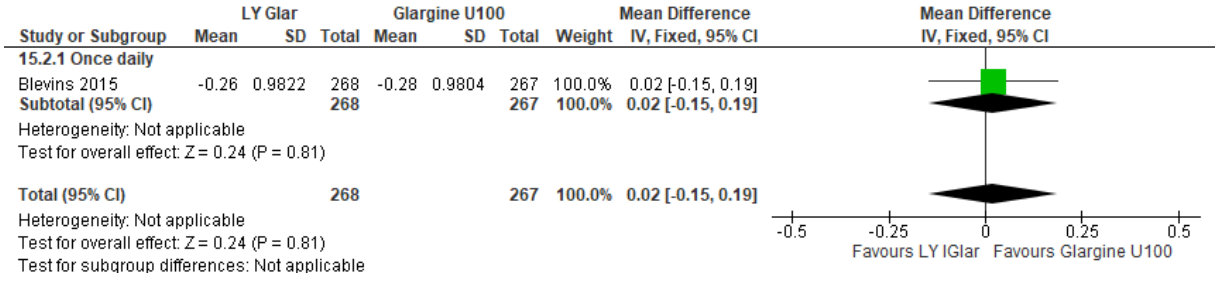
(MD less than 0 favours once daily LY IGlar)



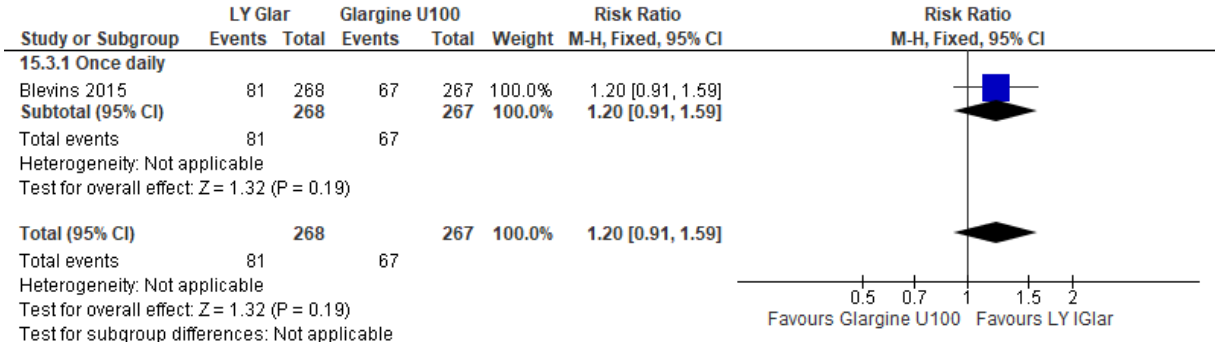
Outcomes > 6 months

Change in HbA1c (%)

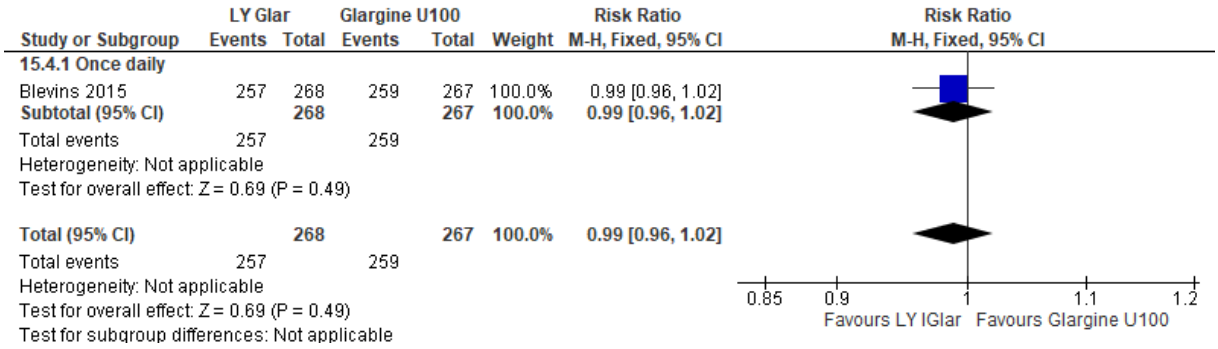
(MD less than 0 favours once daily LY IGlar)



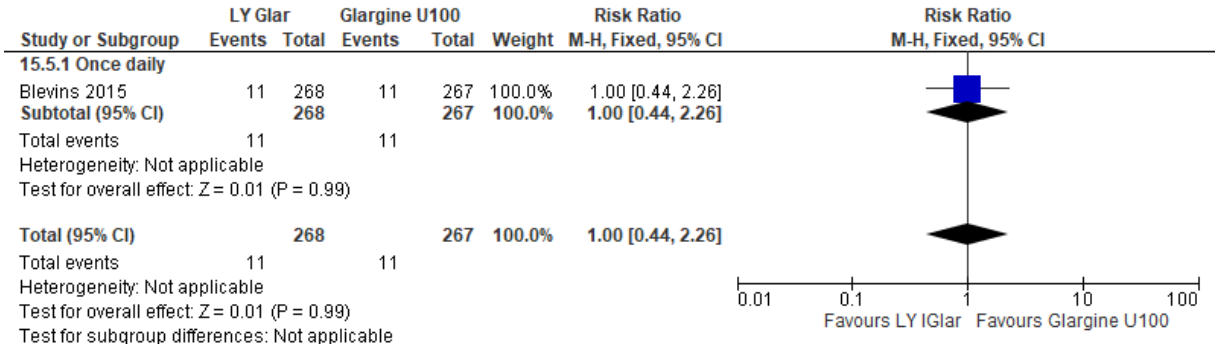
Participants achieving HbA1c <7%



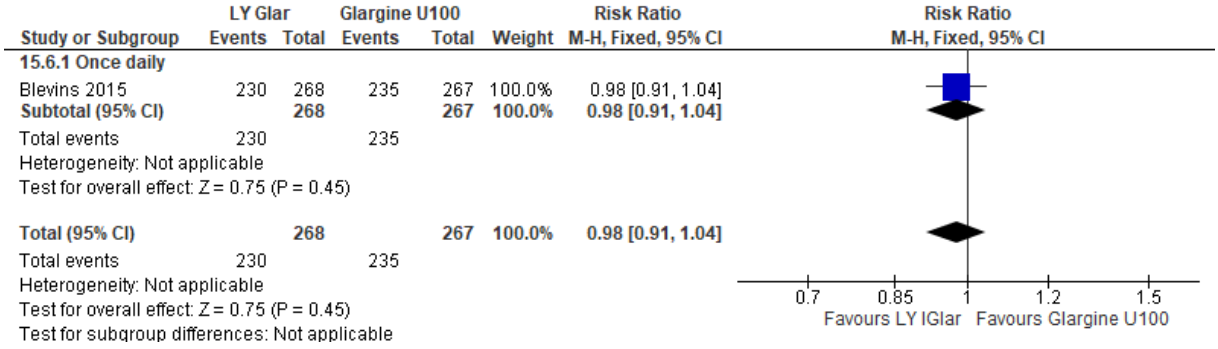
Hypoglycaemia (all)



Major/ Severe hypoglycaemia

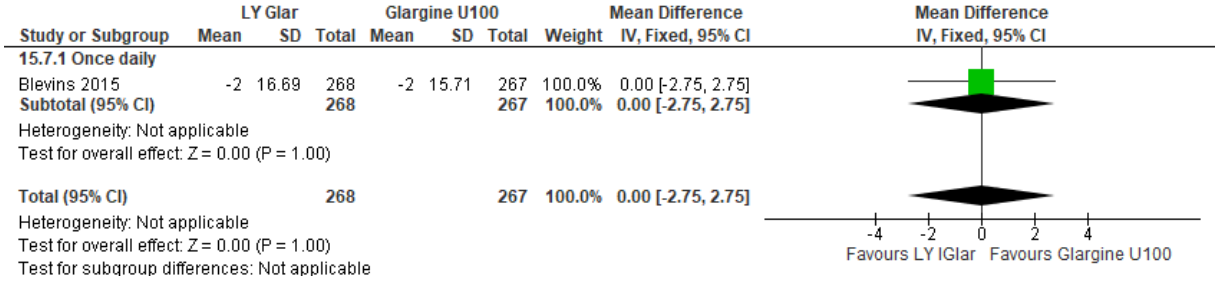


Nocturnal hypoglycaemia

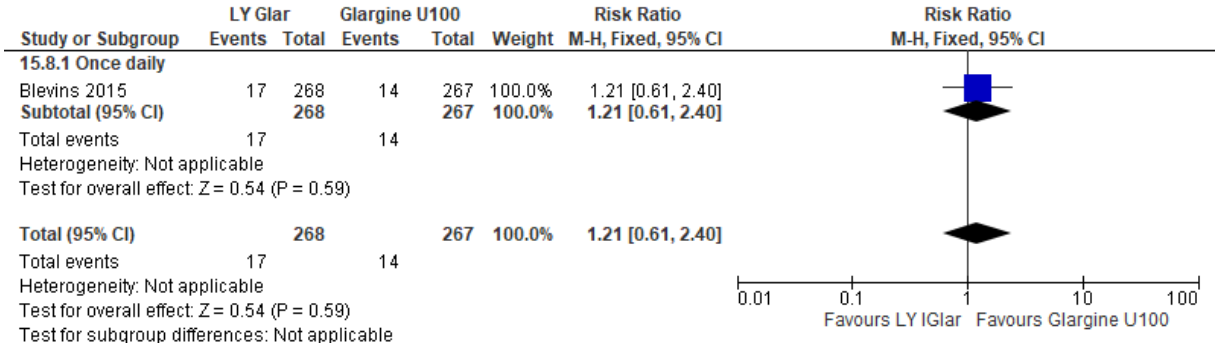


Change in weight (kg)

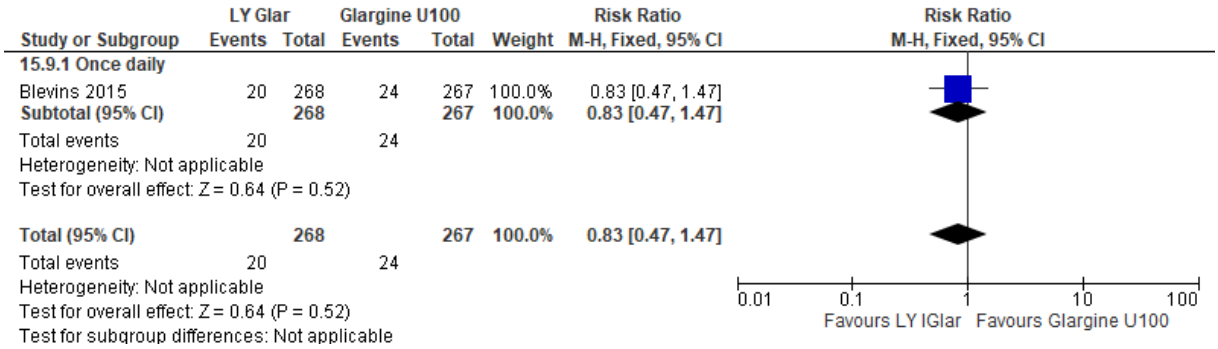
(MD less than 0 favours once daily LY IGlar)



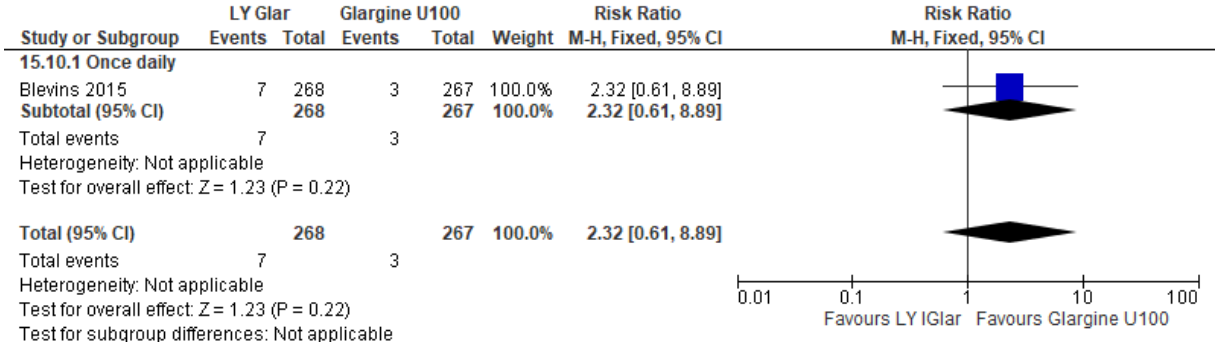
Adverse events



Serious AEs

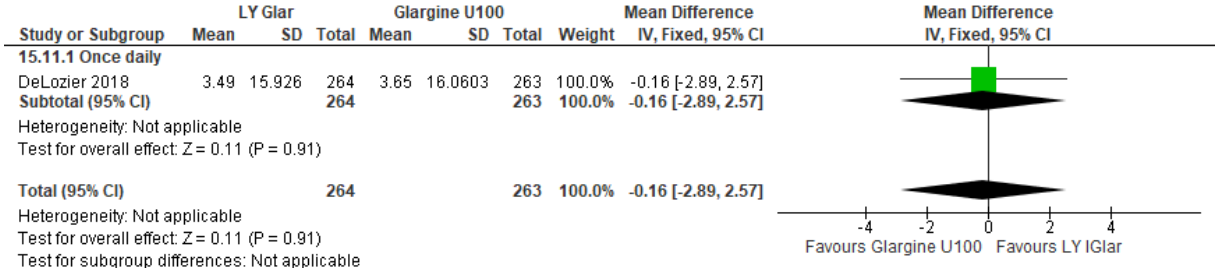


Injection site reaction



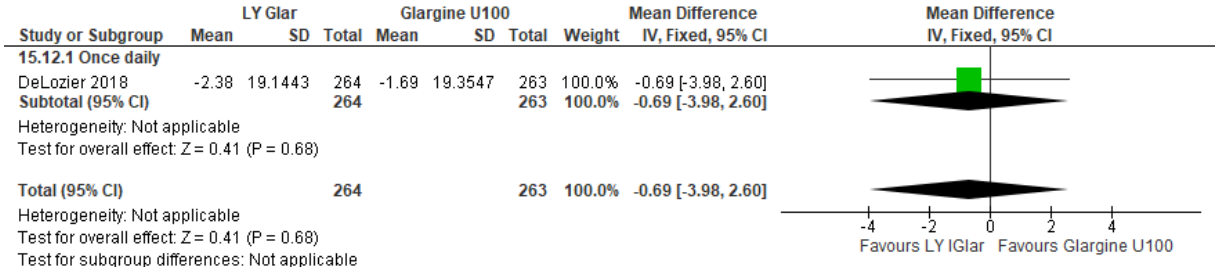
QoL – Change in ITSQ total score

(greater score indicates greater improvement)



QoL – Change in ALBSS total score

(lower score indicates greater improvement)

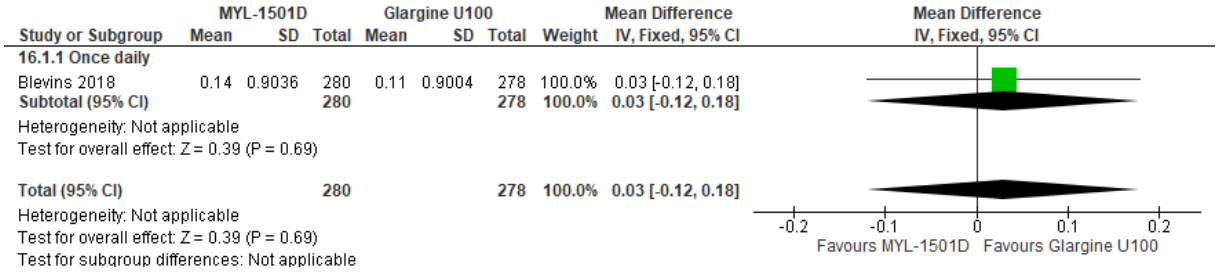


MYLD-1501D vs Glargine U100

Outcomes ≤ 6 months

Change in HbA1c (%)

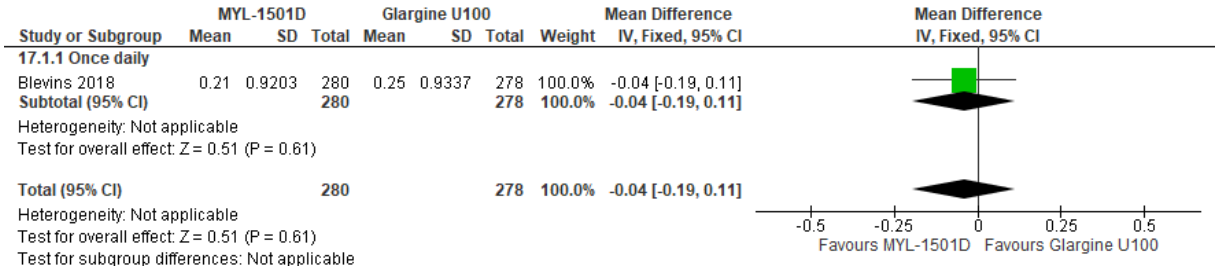
(MD less than 0 favours once daily MYLD-1501D)



Outcomes > 6 months

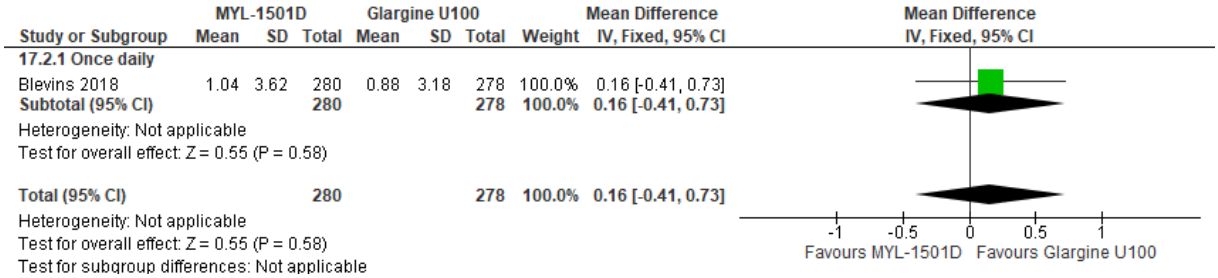
Change in HbA1c (%)

(MD less than 0 favours once daily MYLD-1501D)

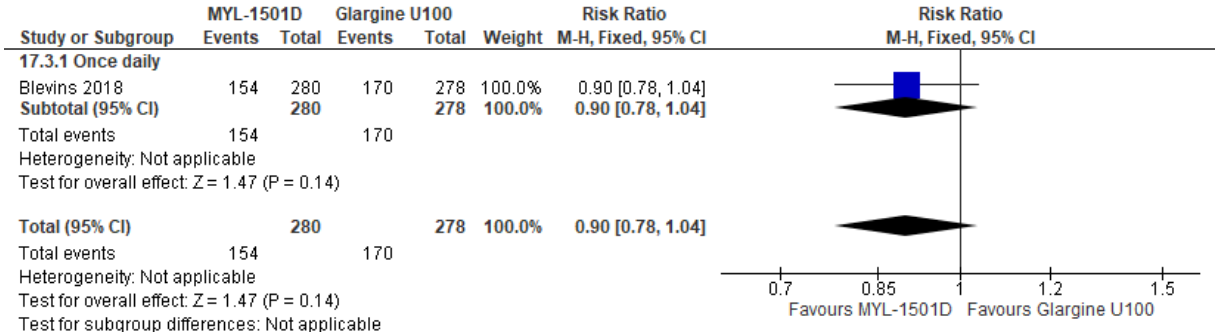


Change in weight (kg)

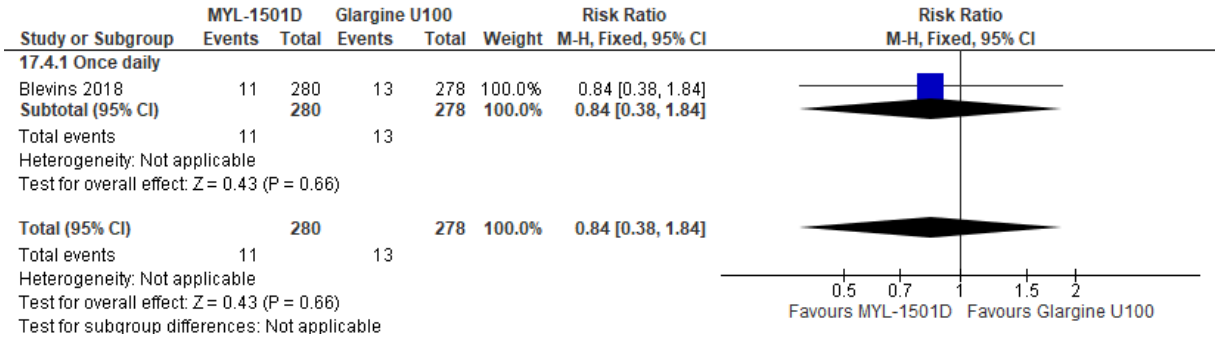
(MD less than 0 favours once daily MYLD-1501D)



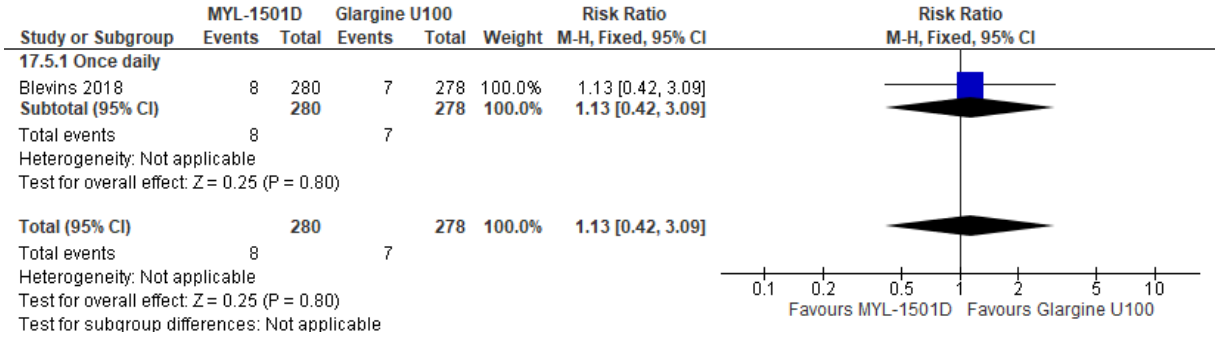
Hypoglycaemia (all)



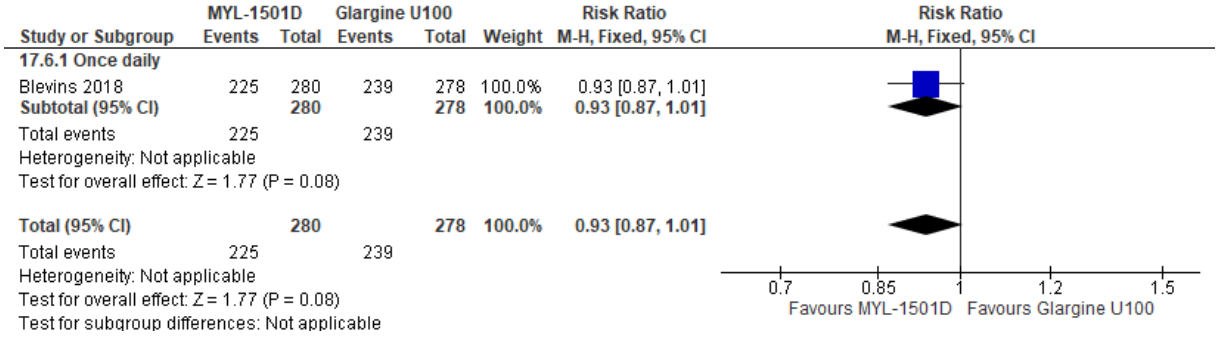
Major/ severe hypoglycaemia



Nocturnal hypoglycaemia



Adverse events

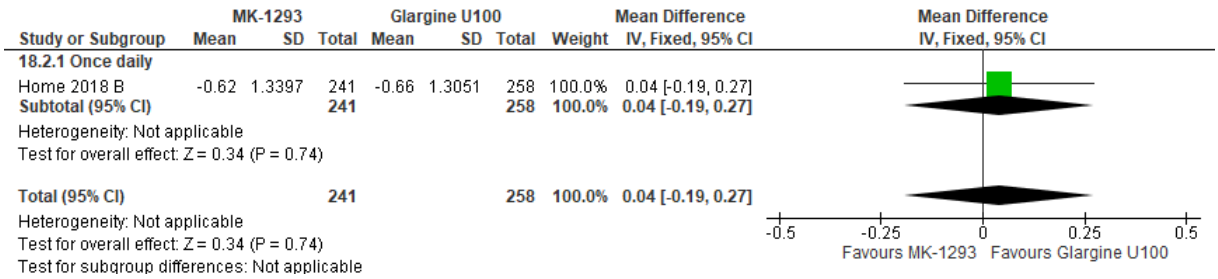


MK-1239 vs Glargine U100

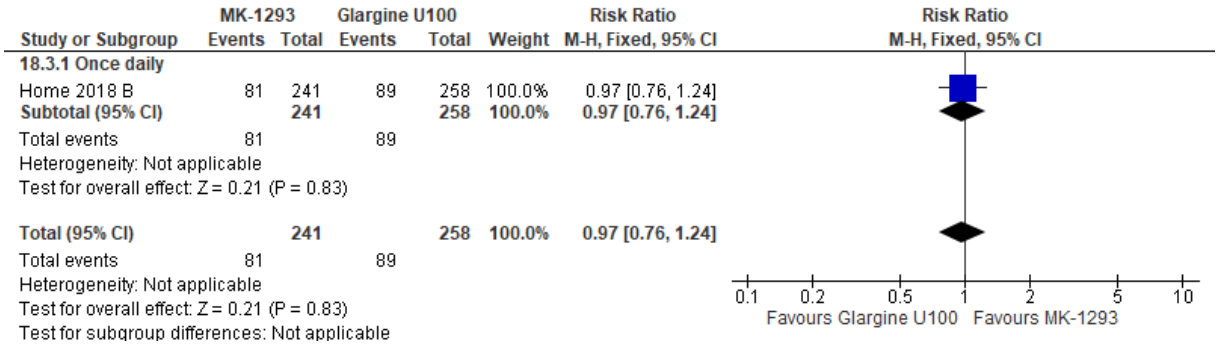
Outcomes ≤ 6 months

Change in HbA1c (%)

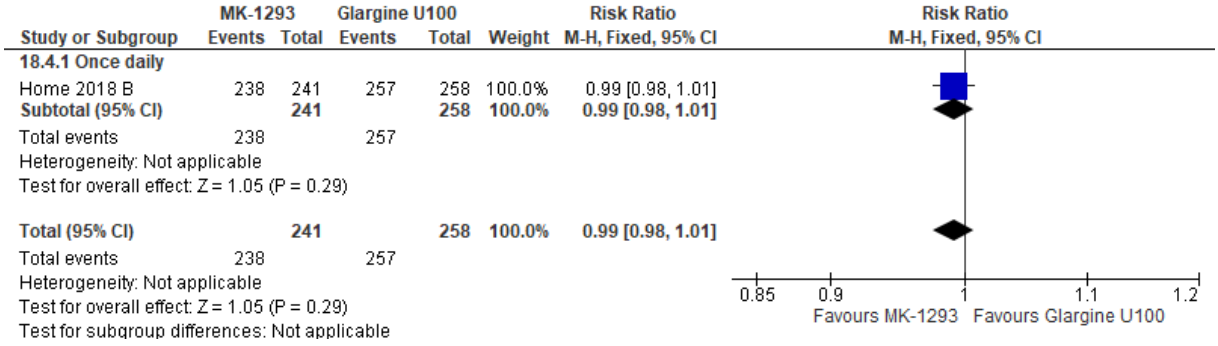
(MD less than 0 favours once daily MK-1239)



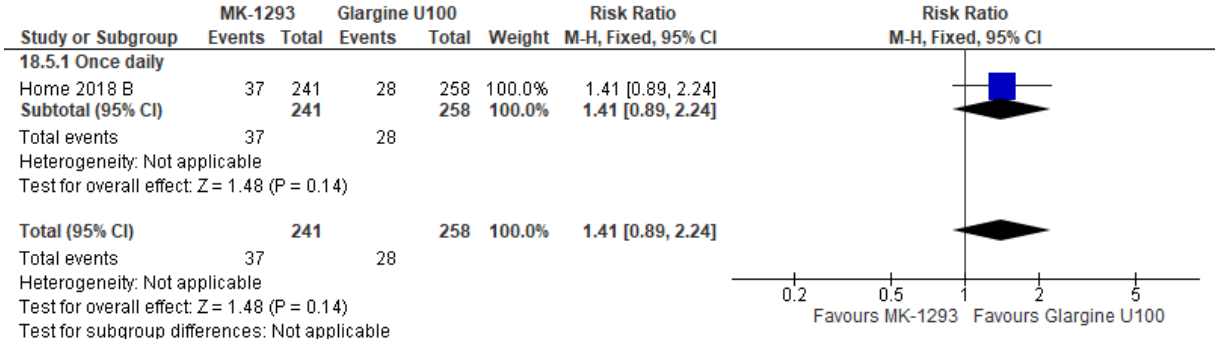
Participants achieving HbA1c <7%



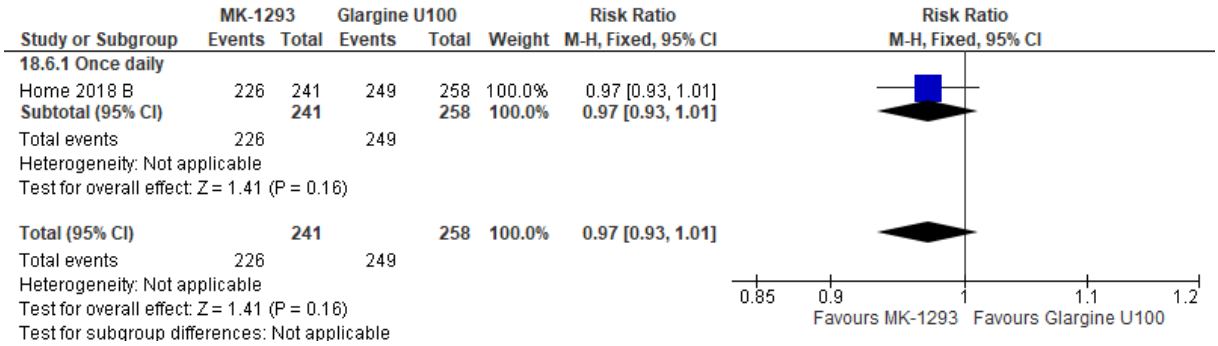
Hypoglycaemia (all)



Major/ severe hypoglycaemia

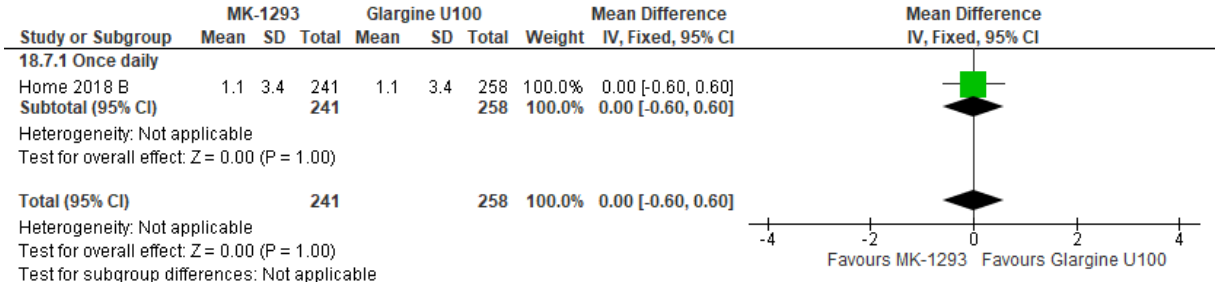


Nocturnal hypoglycaemia



Change in weight (kg)

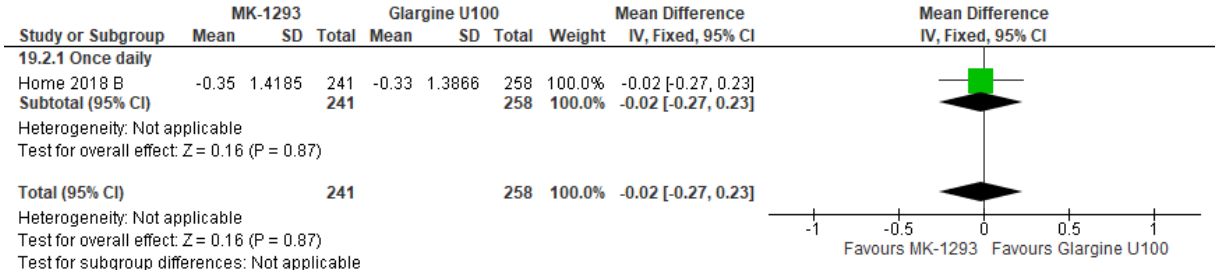
(MD less than 0 favours once daily MK-1239)



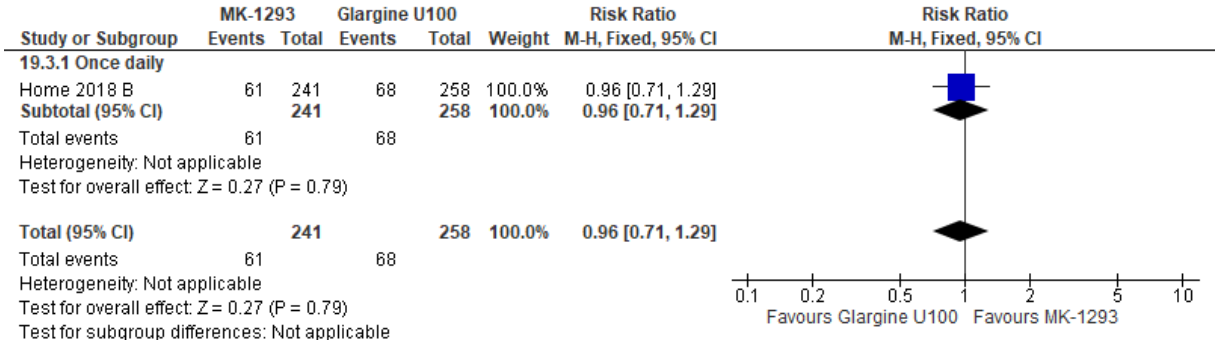
Outcomes > 6 months

Change in HbA1c (%)

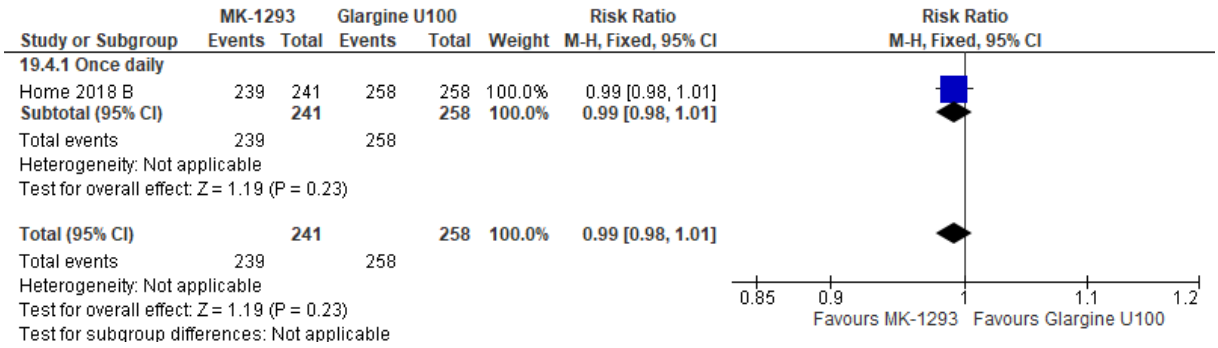
(MD less than 0 favours once daily MK-1239)



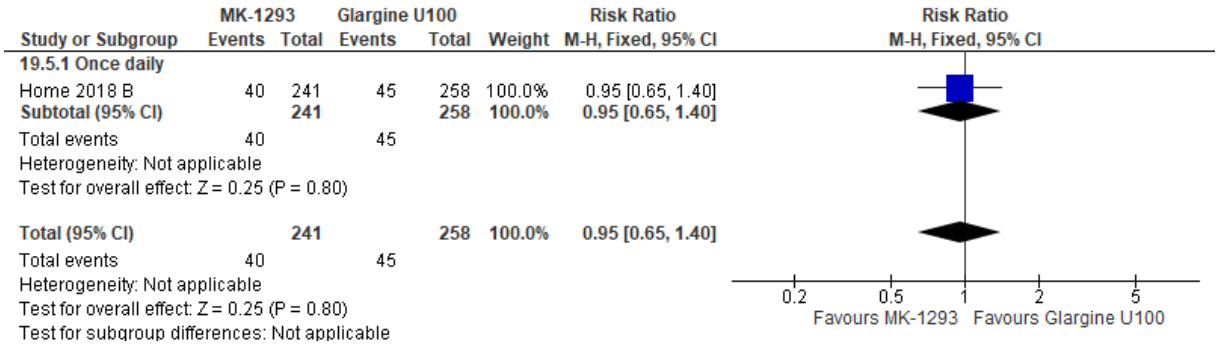
Participants achieving HbA1c <7%



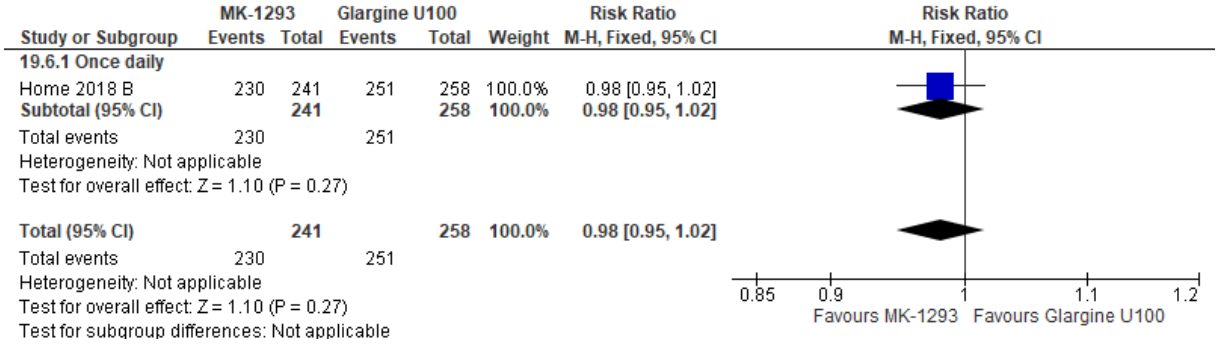
Hypoglycaemia (all)



Major/ severe hypoglycaemia

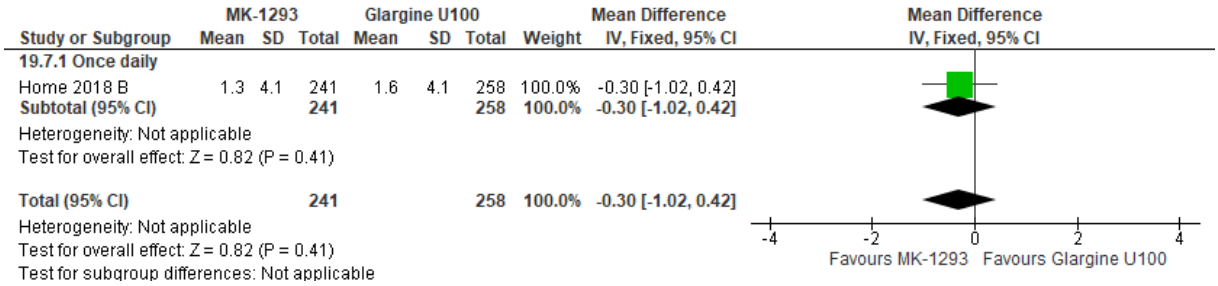


Nocturnal hypoglycaemia

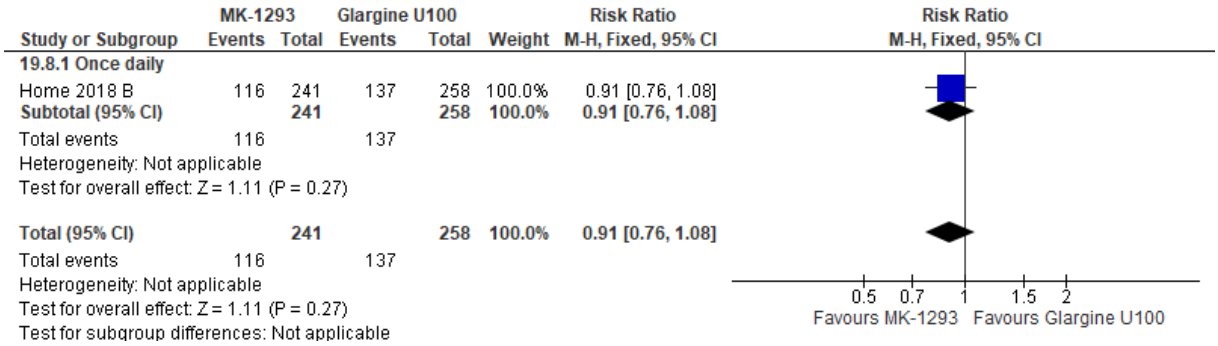


Change in weight (kg)

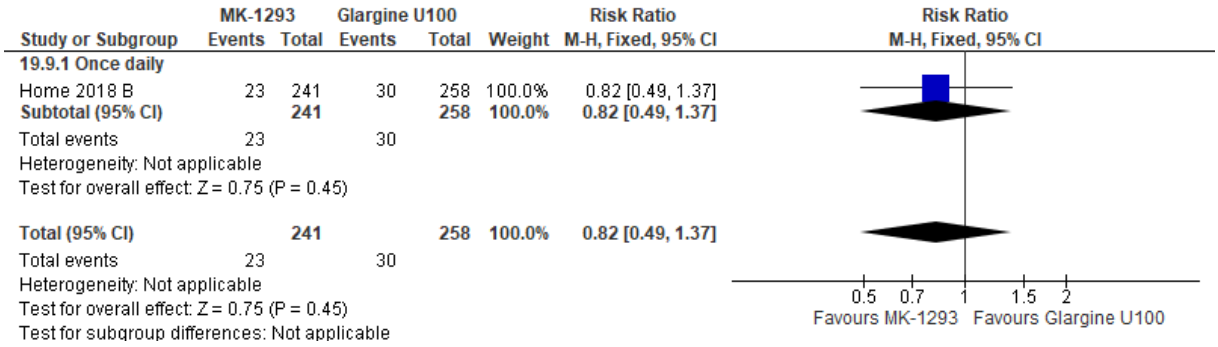
(MD less than 0 favours once daily MK-1239)



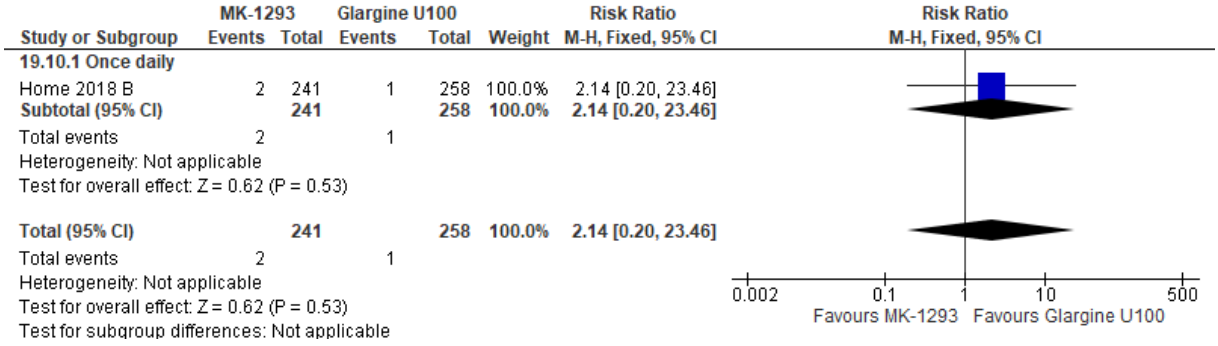
Adverse events



Serious AEs



Injection site reactions

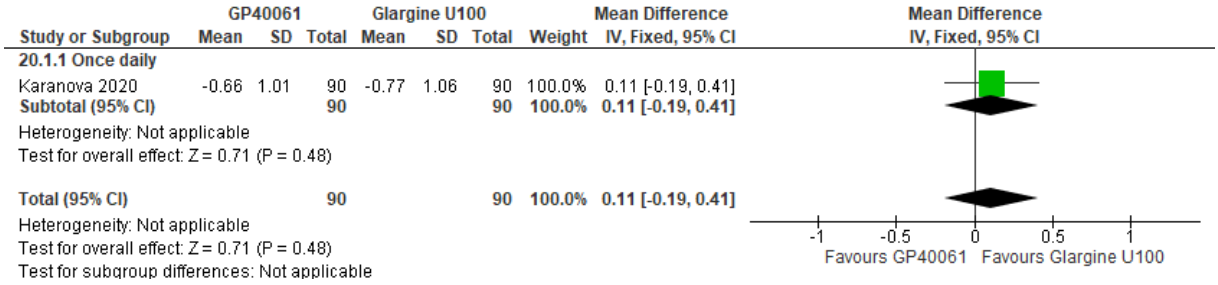


GP40061 vs Glargine U100

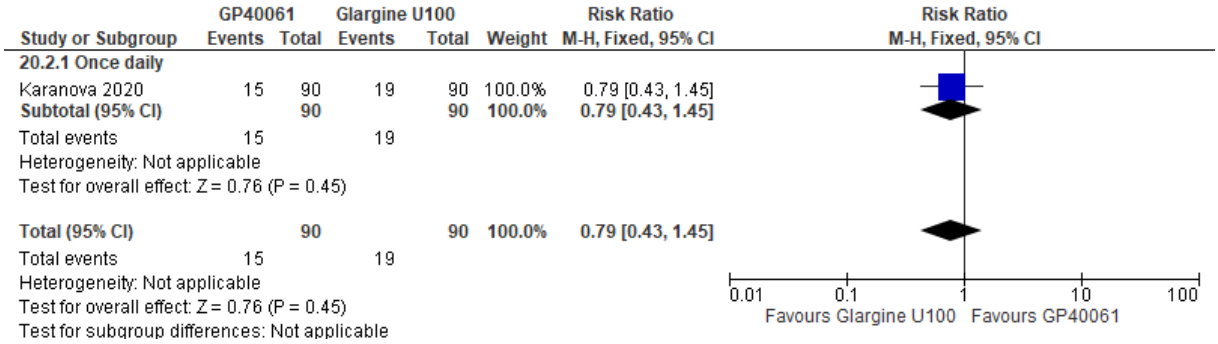
Outcomes ≤ 6 months

Change in HbA1c (%)

(MD less than 0 favours once daily GP40061)

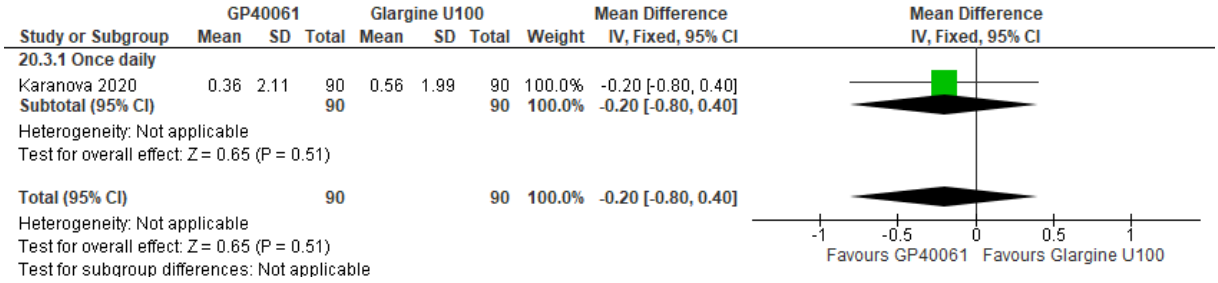


Participants achieving glycaemic control

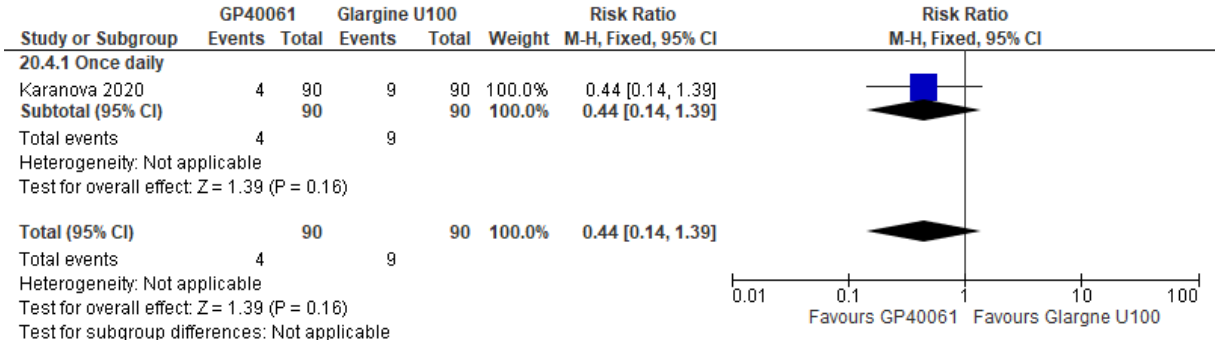


Change in weight (kg)

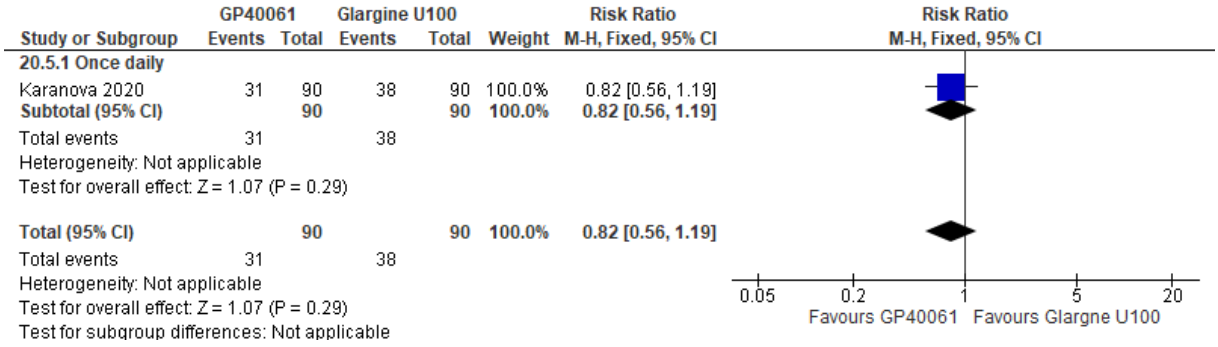
(MD less than 0 favours once daily GP40061)



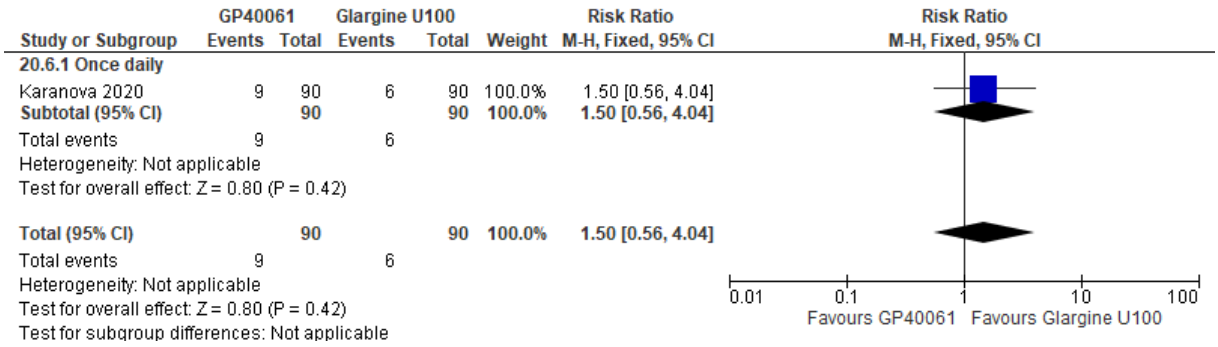
Major/ severe hypoglycaemia



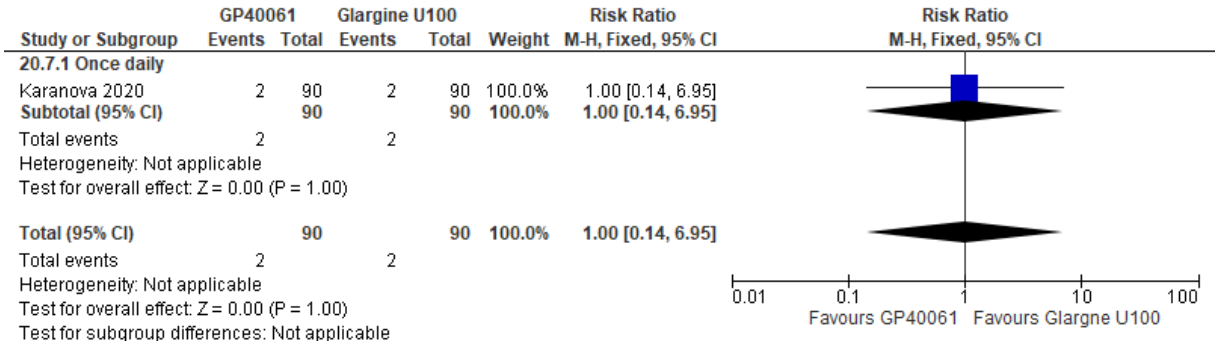
Nocturnal hypoglycaemia



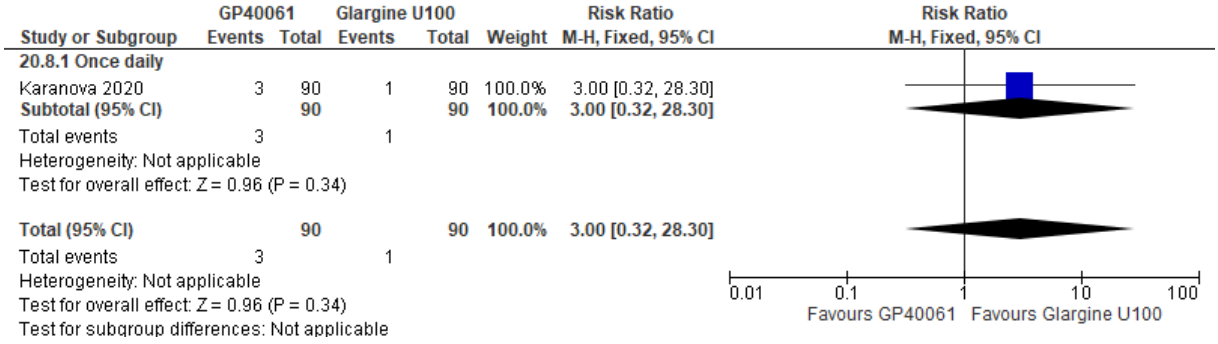
Adverse events



Serious AEs

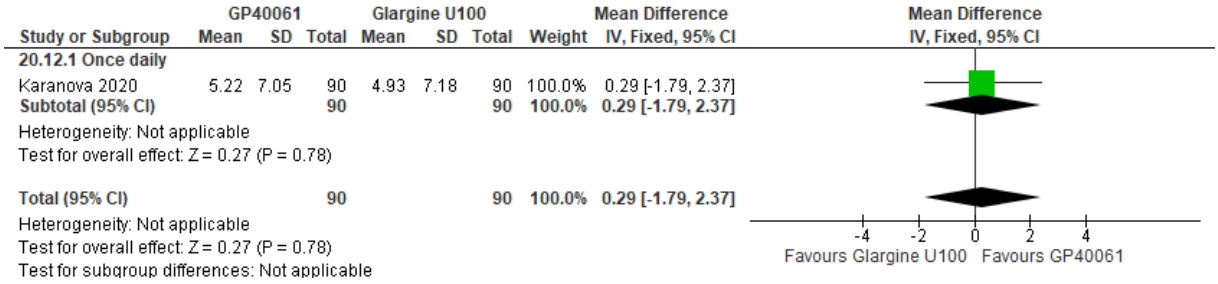


Injection site reactions



QoL – Change in DTSQ total score

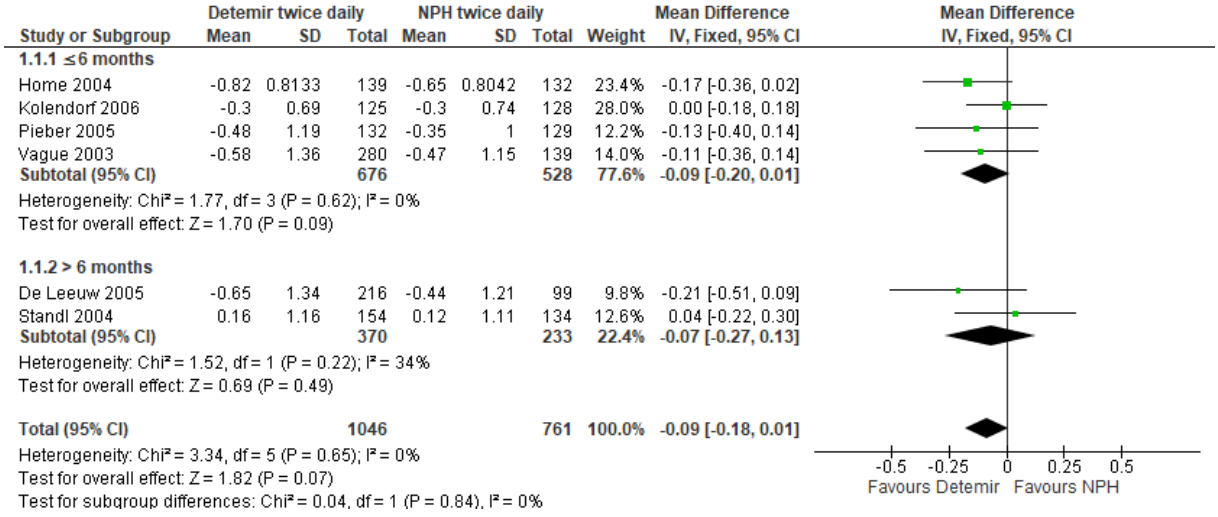
(higher score indicating greater satisfaction)



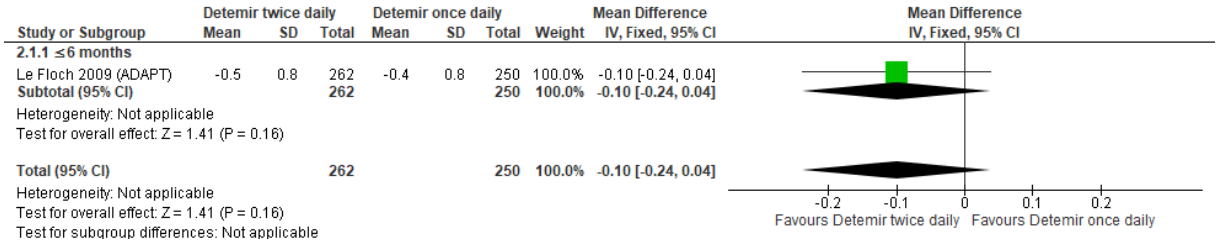
Appendix G – Forest plots for NMA pairwise analysis

Change in HbA1c

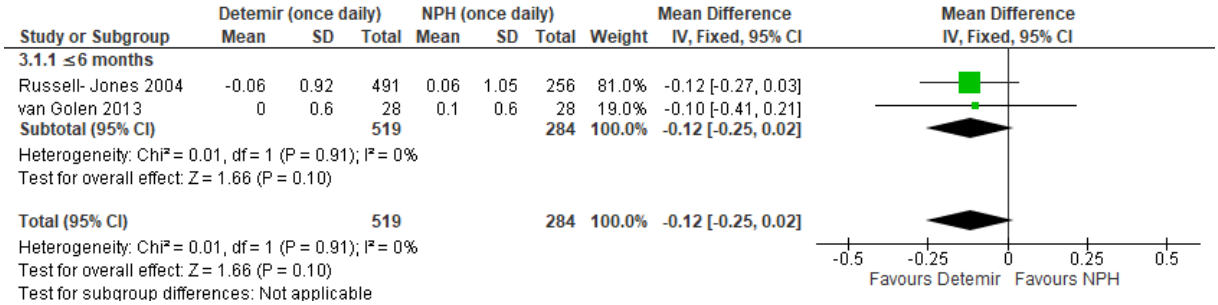
Detemir (Twice daily) vs NPH (Twice daily)



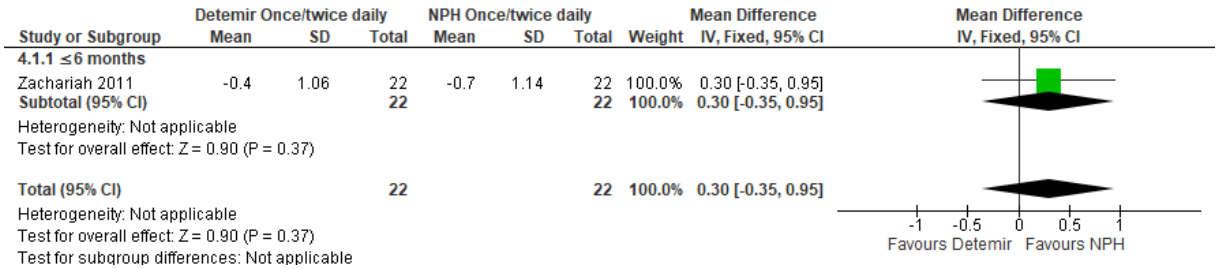
Detemir (Twice daily) vs Detemir (Once daily)



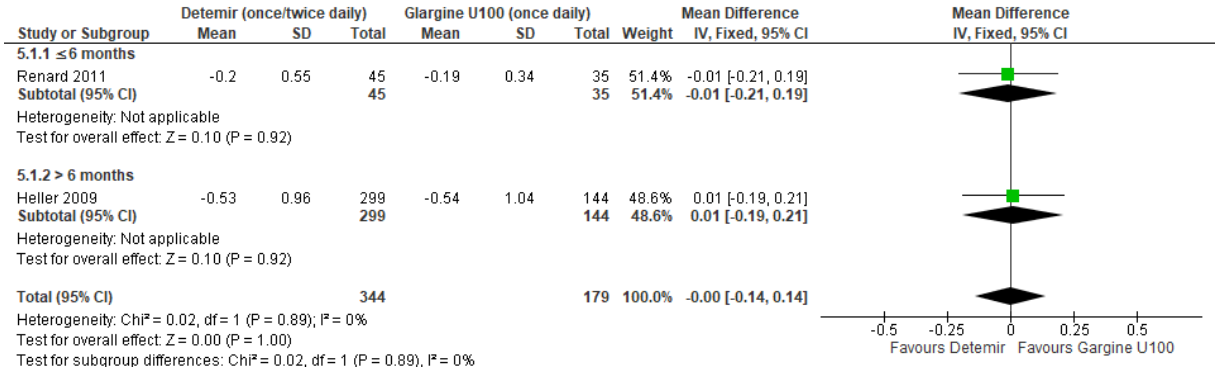
Detemir (Once daily vs NPH (Once daily)



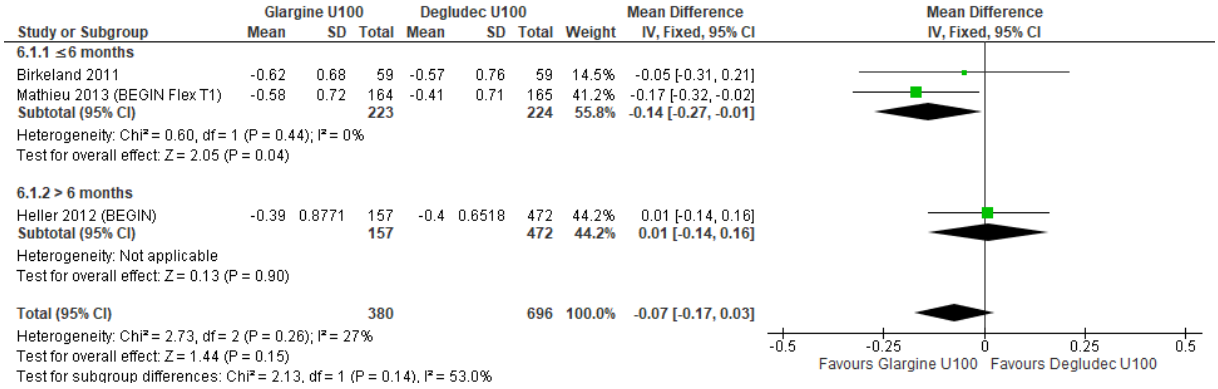
Detemir (Once/twice daily) vs NPH (Once/twice daily)



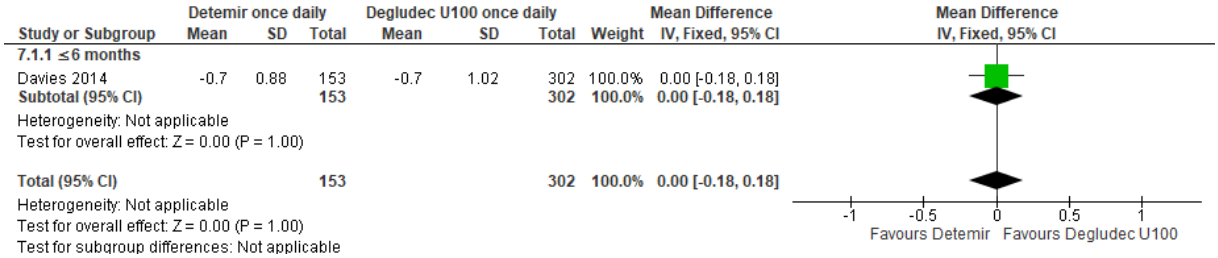
Detemir (Once/twice daily) vs Glargine U100 (Once daily)



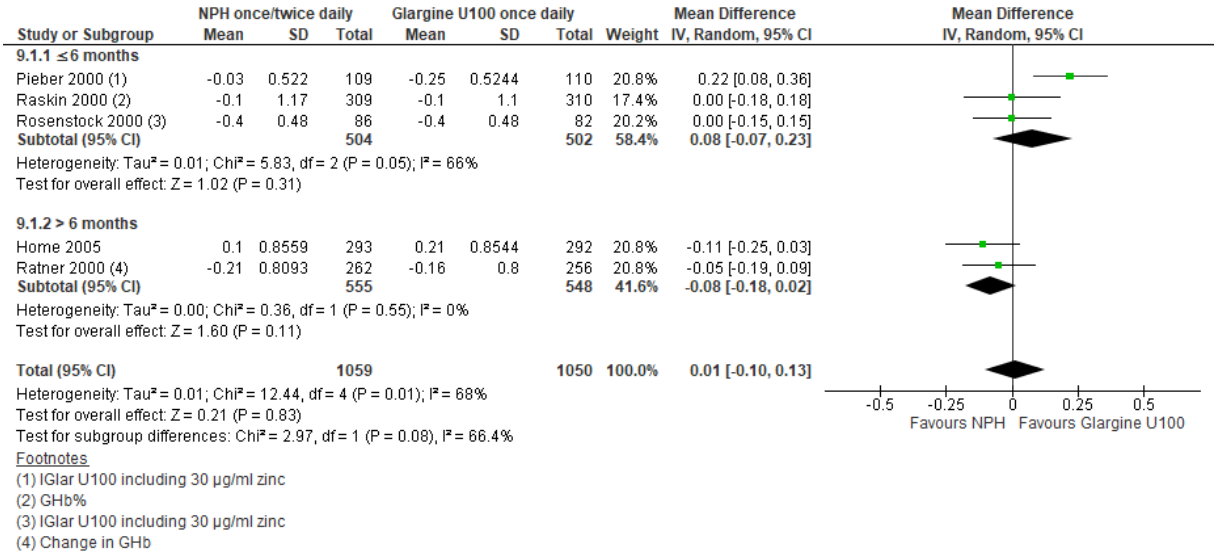
Glargine U100 (Once daily) vs Degludec U100 (Once daily)



Detemir (Once daily) vs Degludec U100 (once daily)



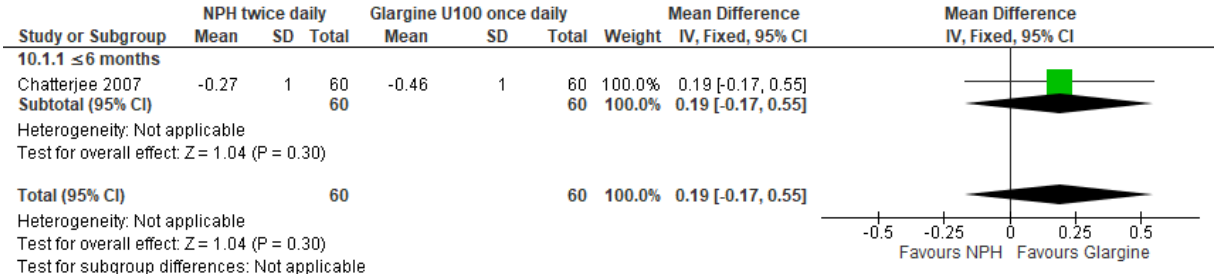
NPH (Once/twice daily) vs Glargine U100 (Once daily)



Study or Subgroup	NPH once/twice daily Mean	SD	Total	Glargine U100 once daily Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
9.1.1 ≤6 months								
Pieber 2000 (1)	-0.03	0.522	109	-0.25	0.5244	110	20.8%	0.22 [0.08, 0.36]
Raskin 2000 (2)	-0.1	1.17	309	-0.1	1.1	310	17.4%	0.00 [-0.18, 0.18]
Rosenstock 2000 (3)	-0.4	0.48	86	-0.4	0.48	82	20.2%	0.00 [-0.15, 0.15]
Subtotal (95% CI)			**504**			**502**	**58.4%**	**0.08 [-0.07, 0.23]**
Heterogeneity: Tau² = 0.01; Chi² = 5.83, df = 2 (P = 0.05); I² = 66%								
Test for overall effect: Z = 1.02 (P = 0.31)								
9.1.2 > 6 months								
Home 2005	0.1	0.8559	293	0.21	0.8544	292	20.8%	-0.11 [-0.25, 0.03]
Ratner 2000 (4)	-0.21	0.8093	262	-0.16	0.8	256	20.8%	-0.05 [-0.19, 0.09]
Subtotal (95% CI)			**555**			**548**	**41.6%**	**-0.08 [-0.18, 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%								
Test for overall effect: Z = 1.60 (P = 0.11)								
Total (95% CI)			**1059**			**1050**	**100.0%**	**0.01 [-0.10, 0.13]**
Heterogeneity: Tau² = 0.01; Chi² = 12.44, df = 4 (P = 0.01); I² = 68%								
Test for overall effect: Z = 0.21 (P = 0.83)								
Test for subgroup differences: Chi² = 2.97, df = 1 (P = 0.08), I² = 66.4%								

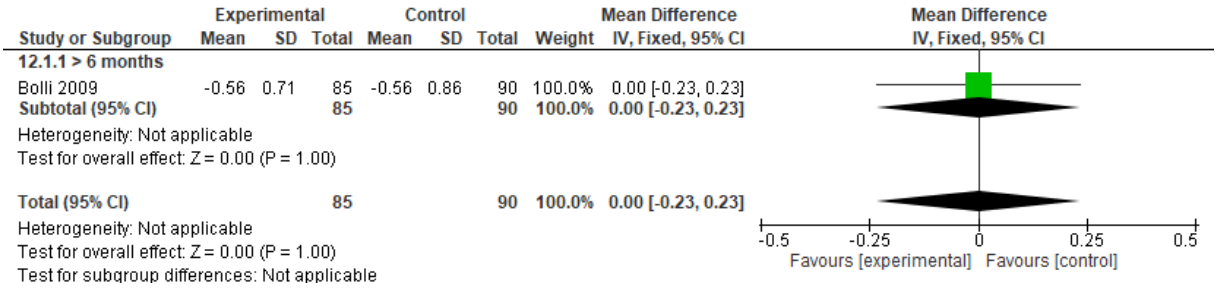
Footnotes
(1) IGlar U100 including 30 µg/ml zinc
(2) GHb%
(3) IGlar U100 including 30 µg/ml zinc
(4) Change in GHb

NPH (Twice Daily) vs Glargine U100 (Once daily)



Study or Subgroup	NPH twice daily Mean	SD	Total	Glargine U100 once daily Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.1.1 ≤6 months								
Chatterjee 2007	-0.27	1	60	-0.46	1	60	100.0%	0.19 [-0.17, 0.55]
Subtotal (95% CI)			**60**			**60**	**100.0%**	**0.19 [-0.17, 0.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.04 (P = 0.30)								
Total (95% CI)			**60**			**60**	**100.0%**	**0.19 [-0.17, 0.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.04 (P = 0.30)								
Test for subgroup differences: Not applicable								

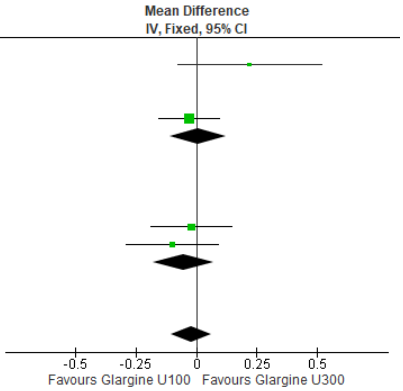
Glargine U100 (Once daily) vs NPH (Twice or more)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
12.1.1 > 6 months								
Bolli 2009	-0.56	0.71	85	-0.56	0.86	90	100.0%	0.00 [-0.23, 0.23]
Subtotal (95% CI)			**85**			**90**	**100.0%**	**0.00 [-0.23, 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**85**			**90**	**100.0%**	**0.00 [-0.23, 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								

Glargine U100 (Once daily) vs Glargine U300 (Once daily)

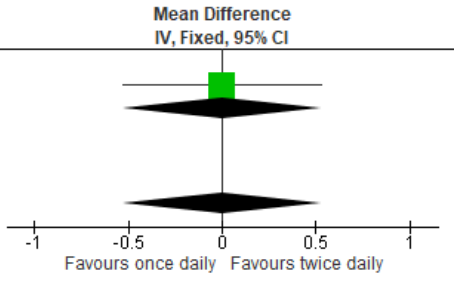
Study or Subgroup	Glargine U100 once daily Mean	SD	Total	Glargine U300 once daily Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
13.1.1 ≤6 months								
Bergenstal 2017	-0.22	0.8826	59	-0.44	0.7675	59	8.1%	0.22 [-0.08, 0.52]
Home 2015 (EDITION 4) (1)	-0.44	0.72	275	-0.42	0.98	274		Not estimable
Matsuhisa 2016 A (EDITION JP 1) (2)	-0.43	0.66	121	-0.3	0.6627	122		Not estimable
Pettus 2019	-0.62	0.73	268	-0.59	0.77	277	45.5%	-0.03 [-0.16, 0.10]
Subtotal (95% CI)			**327**			**336**	**53.7%**	**0.01 [-0.11, 0.12]**
Heterogeneity: Chi² = 2.29, df = 1 (P = 0.13); I² = 56%								
Test for overall effect: Z = 0.13 (P = 0.90)								
13.1.2 > 6 months								
Home 2018 (EDITION 4) (3)	-0.22	0.995	275	-0.2	0.9932	274	26.1%	-0.02 [-0.19, 0.15]
Matsuhisa 2016 B (EDITION JP 1) (4)	-0.3	0.7	121	-0.2	0.8	122	20.2%	-0.10 [-0.29, 0.09]
Subtotal (95% CI)			**396**			**396**	**46.3%**	**-0.05 [-0.18, 0.07]**
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%								
Test for overall effect: Z = 0.86 (P = 0.39)								
Total (95% CI)			**723**			**732**	**100.0%**	**-0.02 [-0.11, 0.06]**
Heterogeneity: Chi² = 3.20, df = 3 (P = 0.36); I² = 6%								
Test for overall effect: Z = 0.49 (P = 0.62)								
Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%								



Footnotes
(1) 6 months - Longest follow up data included in analysis
(2) 6 months- Longest follow up data included in analysis
(3) 12 months
(4) 12 months

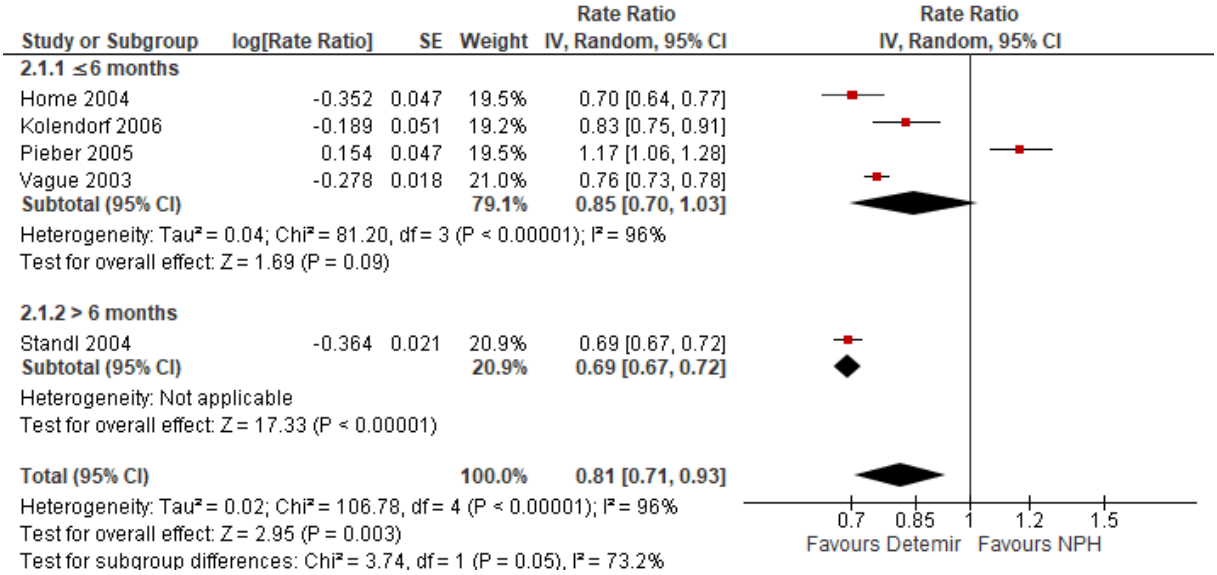
Glargine U100 (Once daily) vs Glargine U100 (Twice daily)

Study or Subgroup	Once daily Mean	SD	Total	Twice daily Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
23.2.1 ≤6 months								
Ashwell 2006	-0.9	0.85	20	-0.9	0.85	20	100.0%	0.00 [-0.53, 0.53]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**0.00 [-0.53, 0.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**20**			**20**	**100.0%**	**0.00 [-0.53, 0.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								

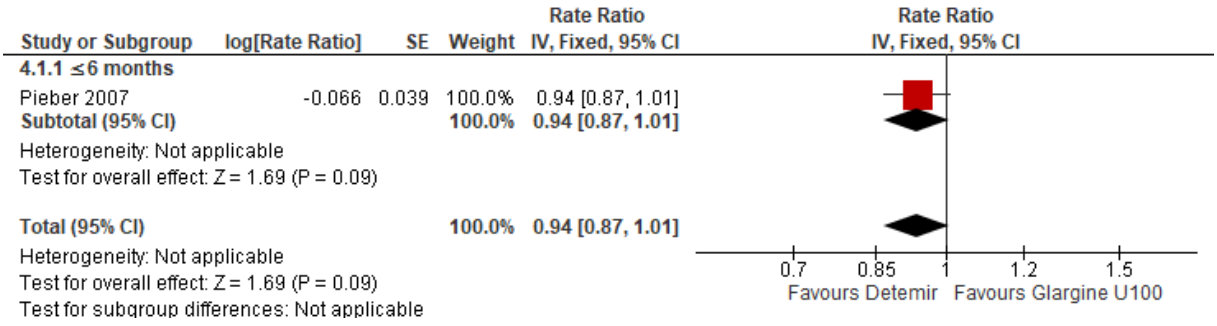


All hypoglycaemia

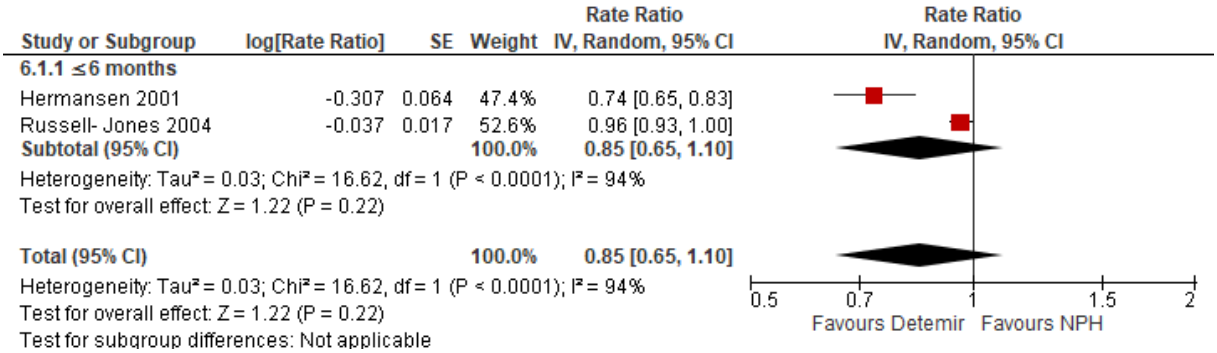
Detemir (Twice daily) vs NPH (Twice daily)



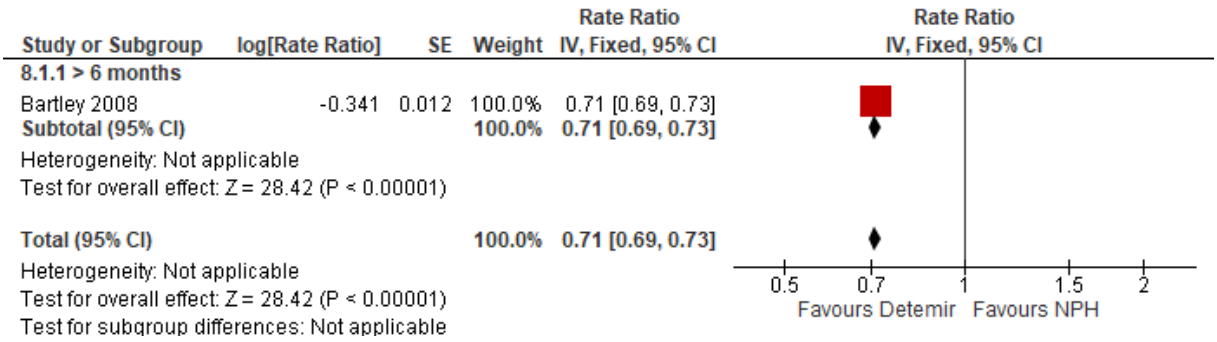
Detemir (Twice daily) vs Glargine U100 (Once daily)



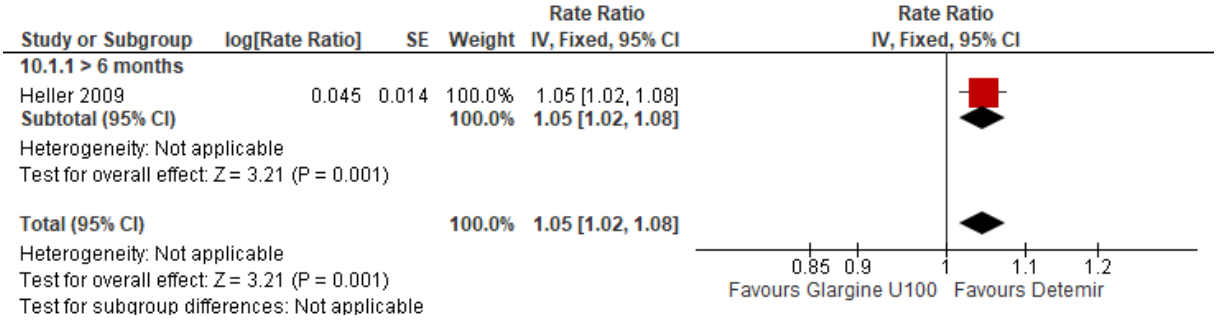
Detemir (Once daily) vs NPH (Once daily)



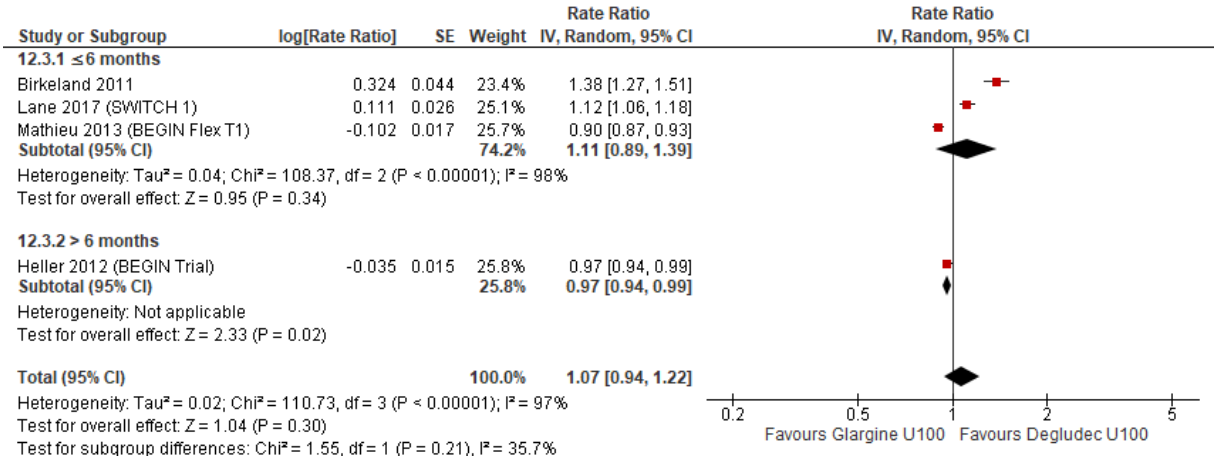
Detemir (Once/twice daily) vs NPH (Once/ twice daily)



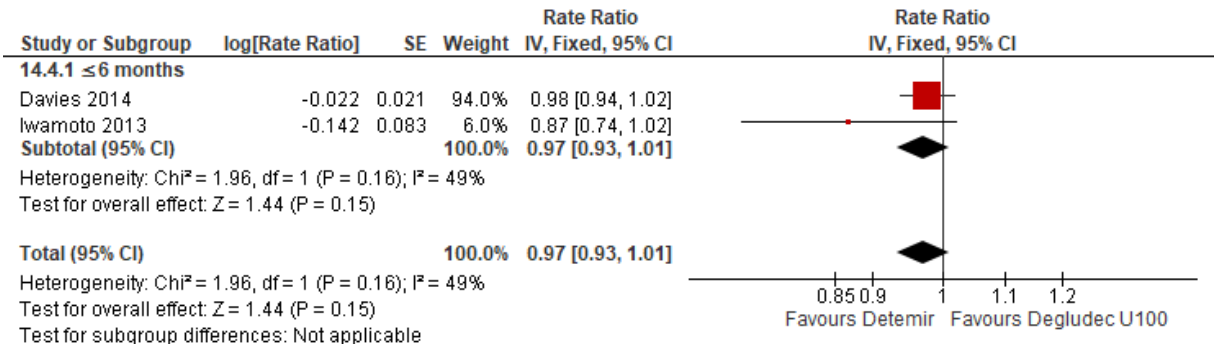
Glargine U100 (Once daily) vs Detemir (Once/Twice daily)



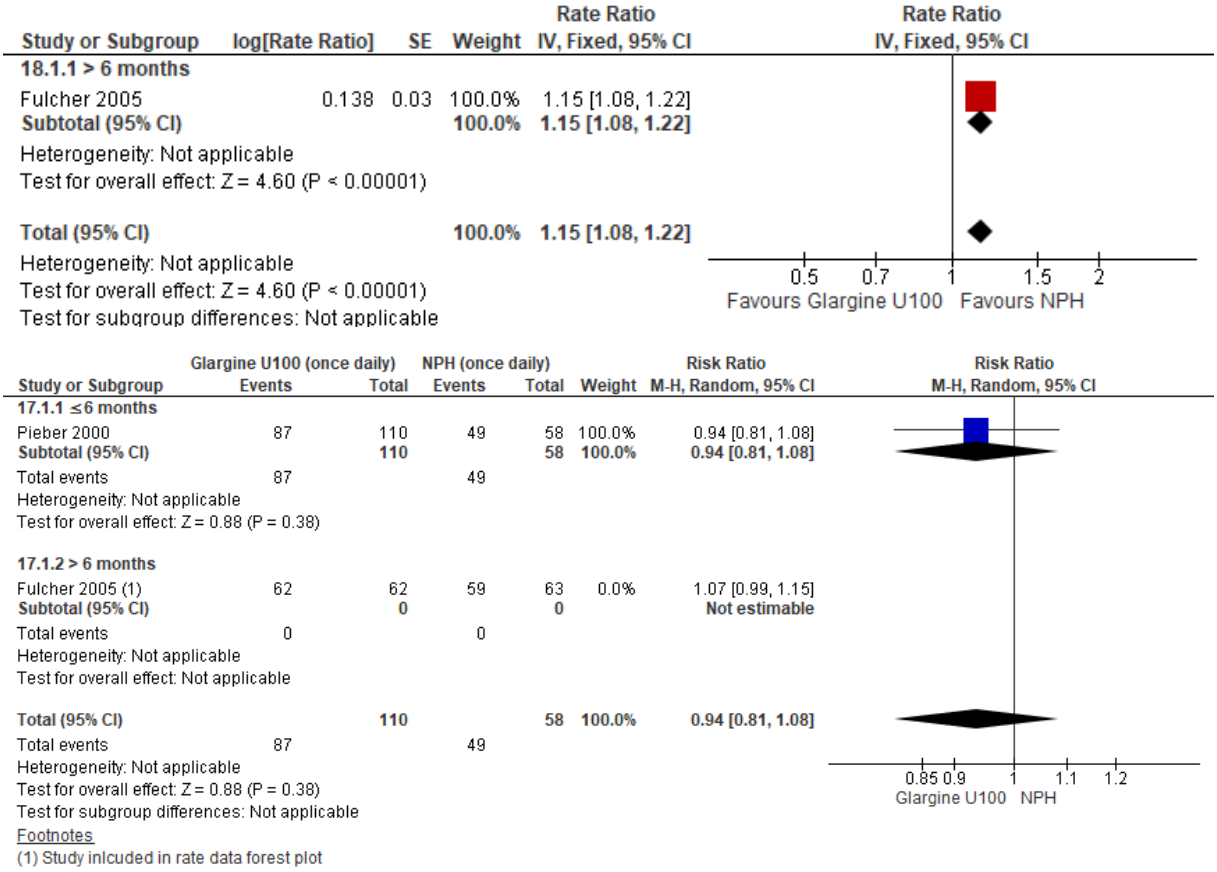
Glargine U100 (Once daily) vs Degludec U100 (Once daily)



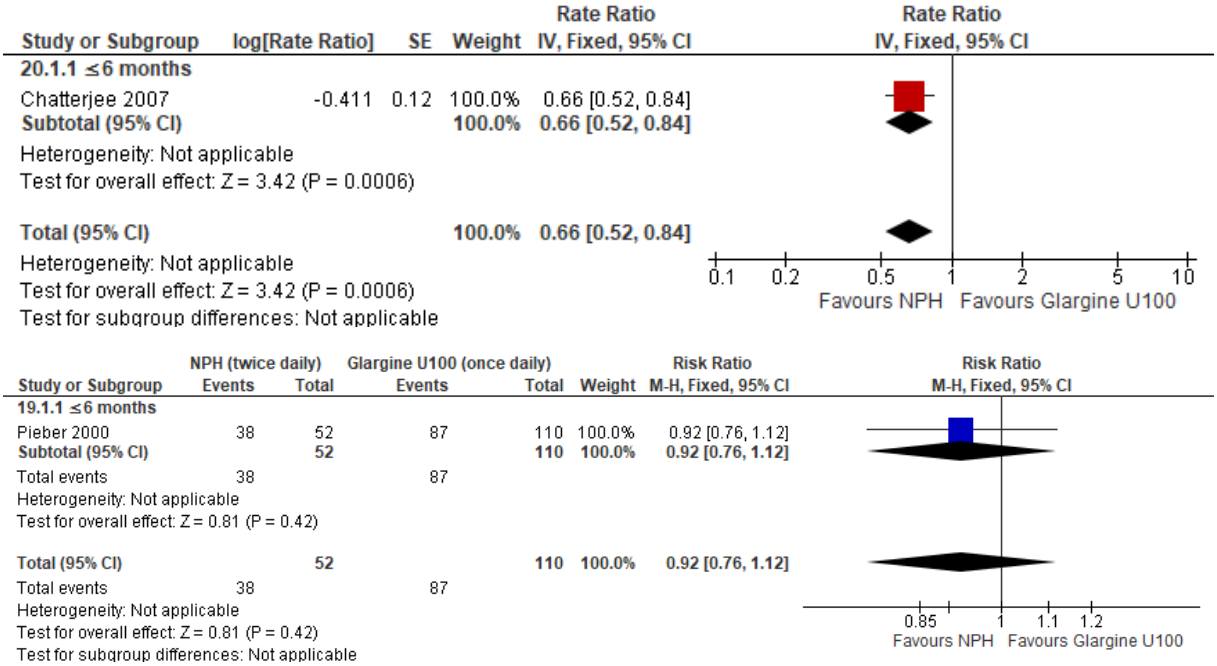
Detemir (Once daily) vs Degludec U100 (Once daily)



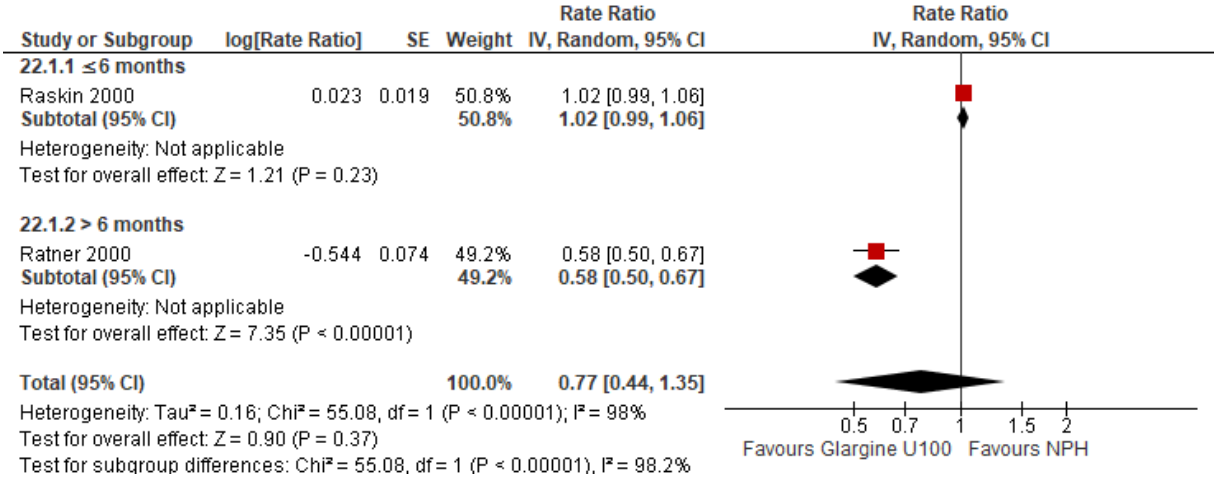
Glargine U100 (Once daily) vs NPH (Once daily)

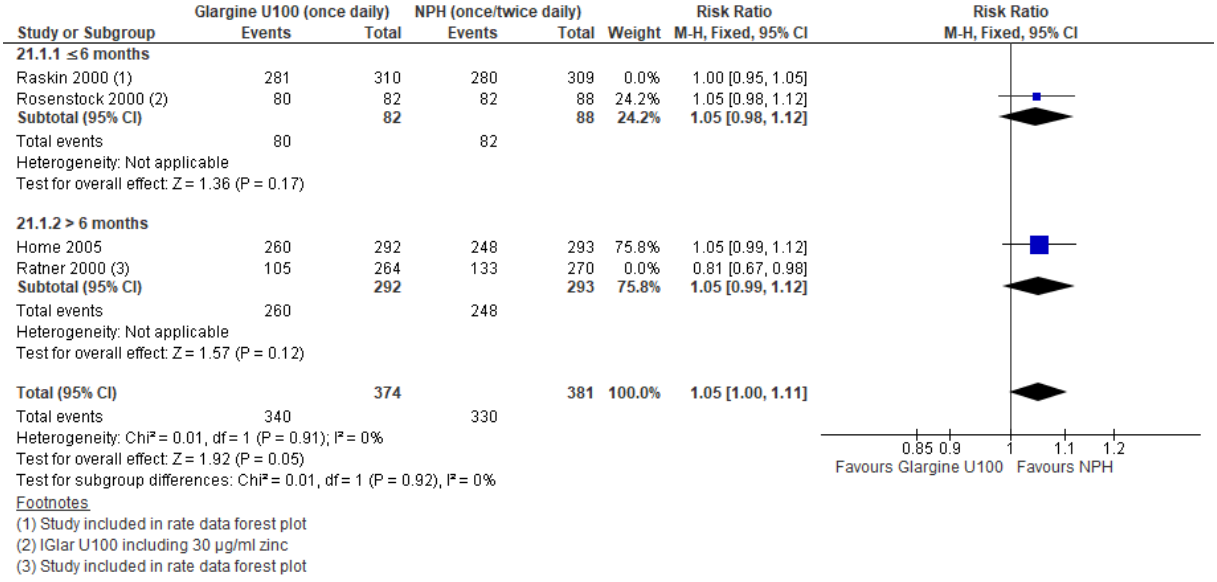


NPH (Twice daily) vs Glargine U100 (Once daily)



Glargine U100 (Once daily) vs NPH (Once/twice daily)





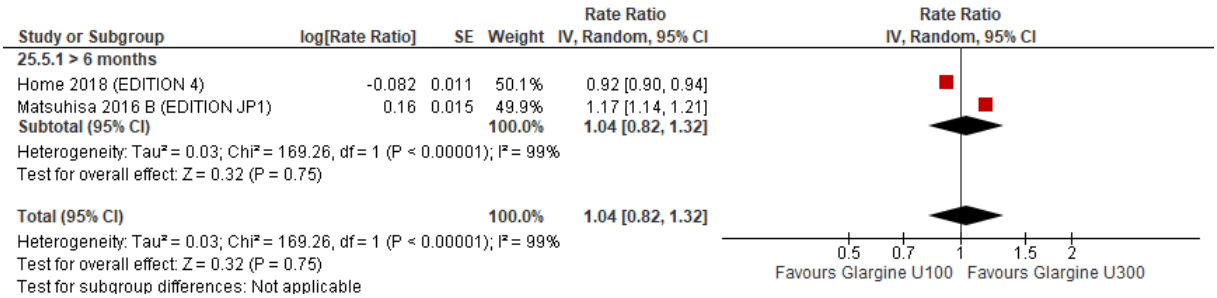
Footnotes

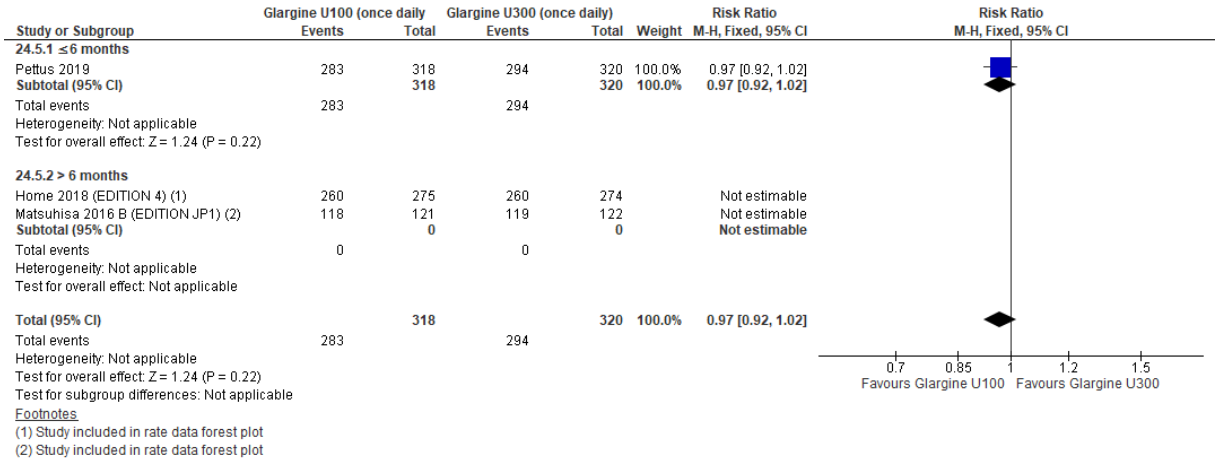
(1) Study included in rate data forest plot

(2) IGlar U100 including 30 µg/ml zinc

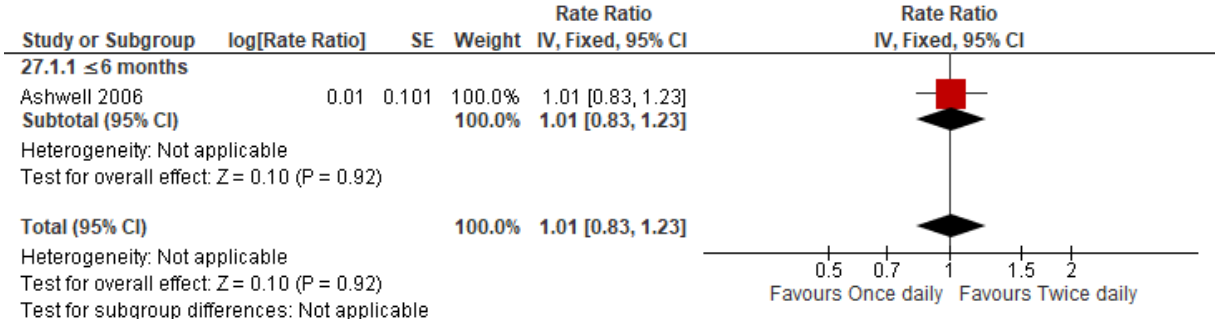
(3) Study included in rate data forest plot

Glargine U100 (Once daily) vs Glargine U300 (Once daily)

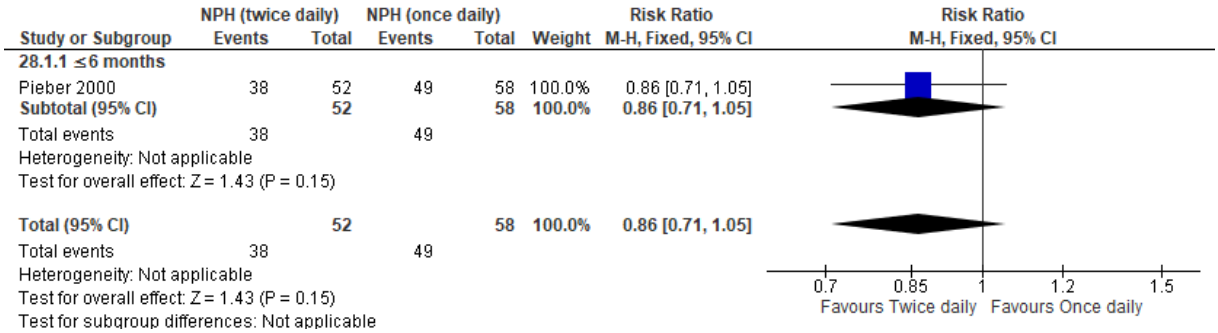




Glaring U100 (Once daily) vs Glargine U100 (Twice daily)

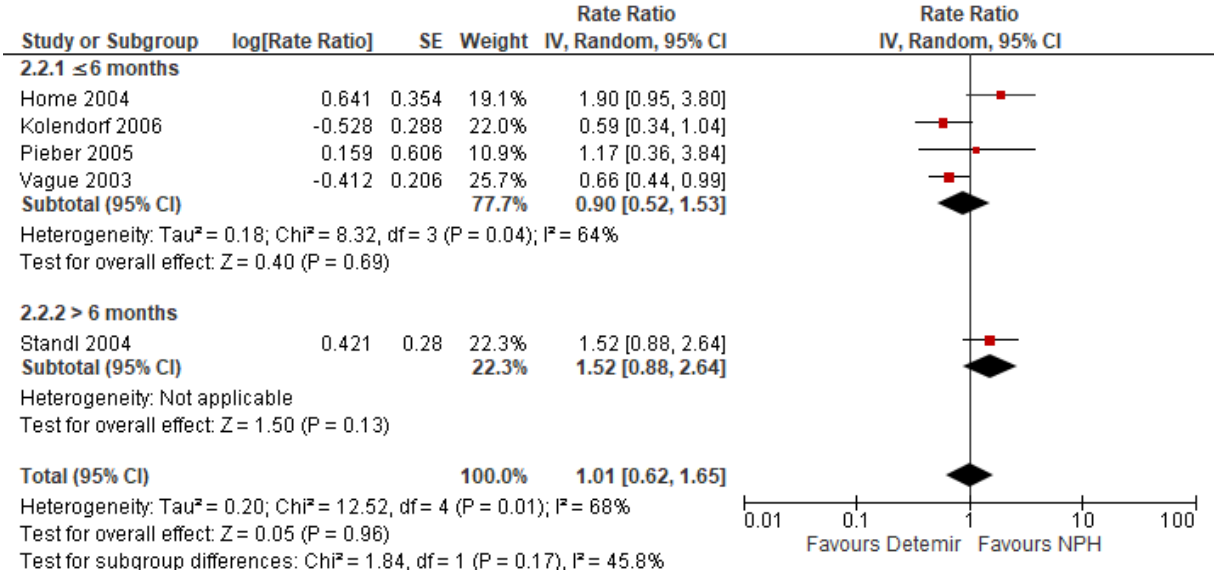


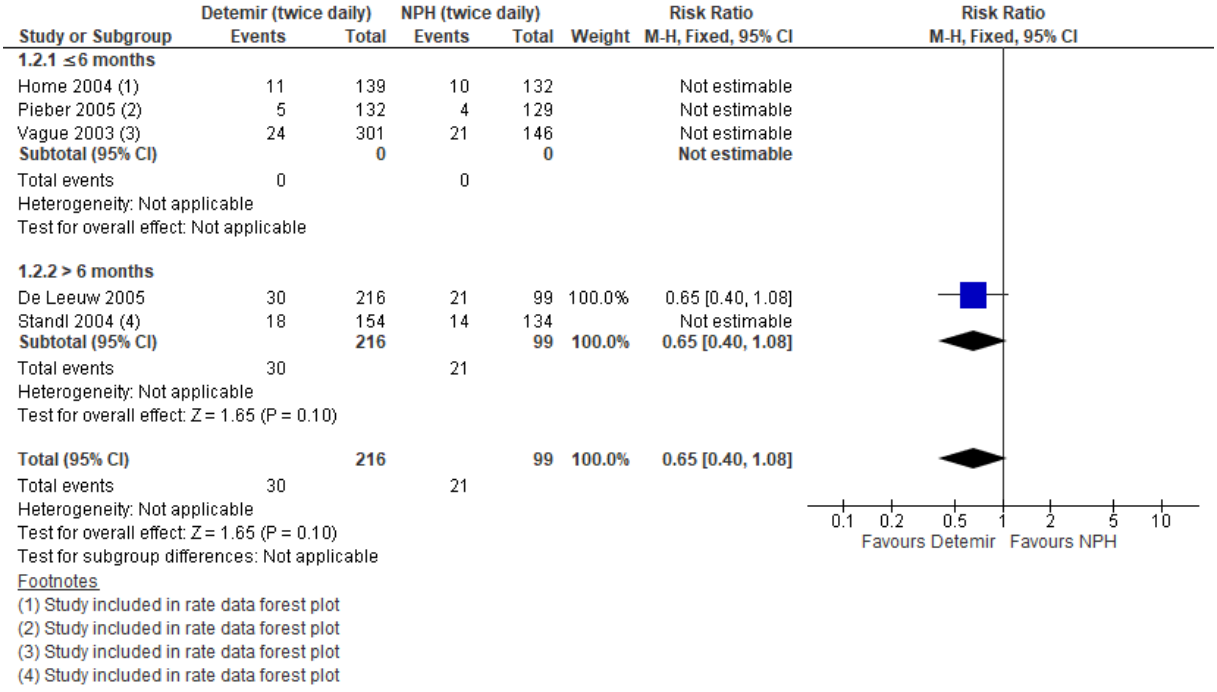
NPH (Twice daily) vs NPH (Once daily)



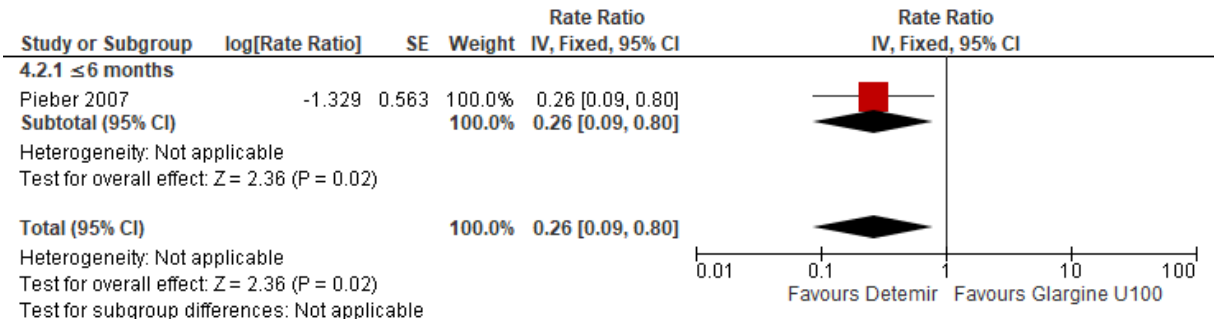
Severe/major hypoglycaemia

Detemir (Twice daily) vs NPH (Twice daily)

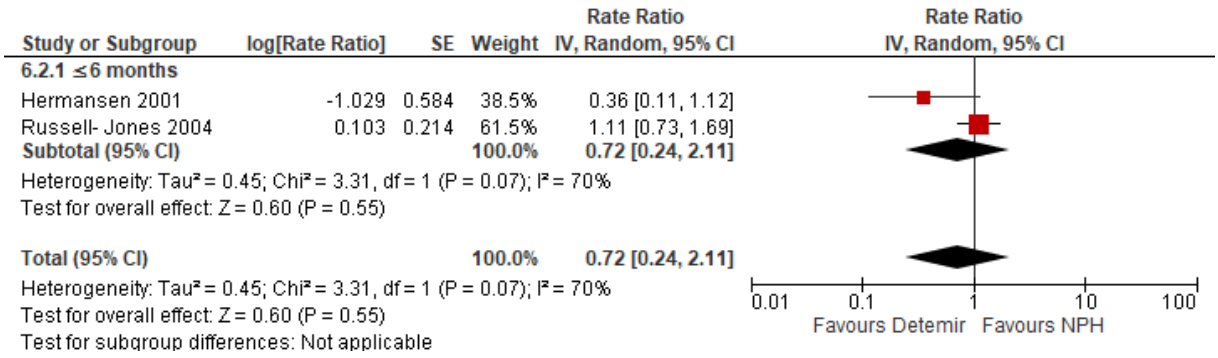




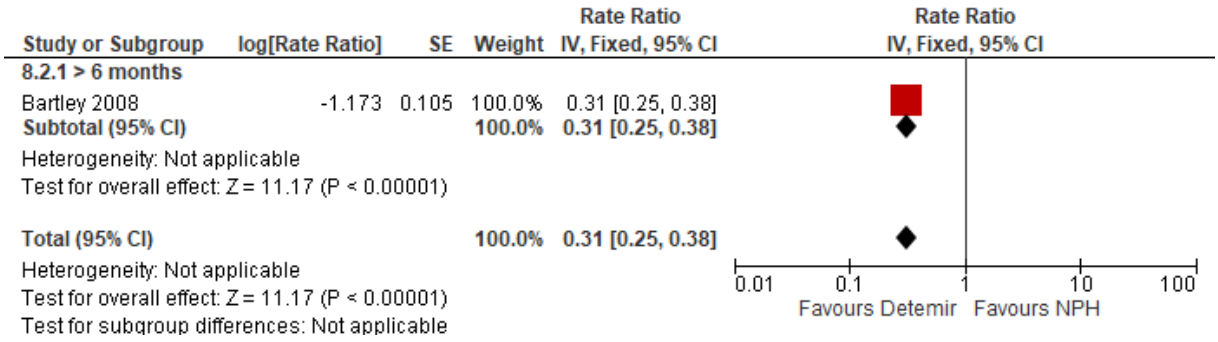
Detemir (Twice daily) vs Glargine U100 (Once daily)



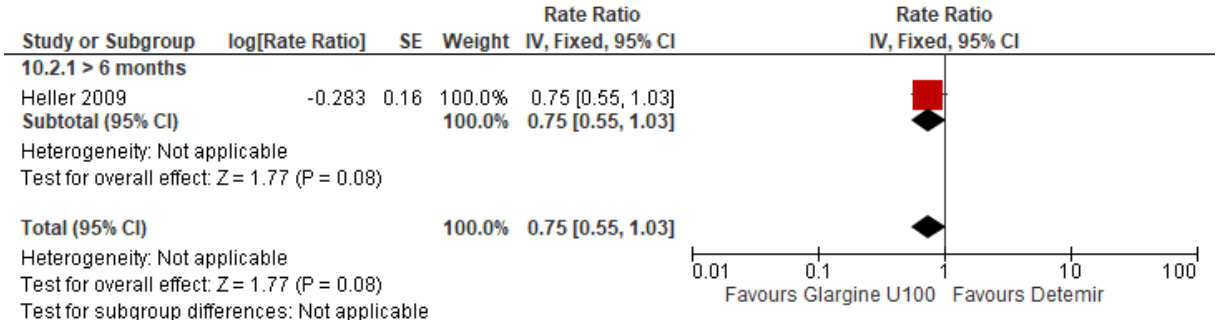
Detemir (Once daily) vs NPH (Once daily)

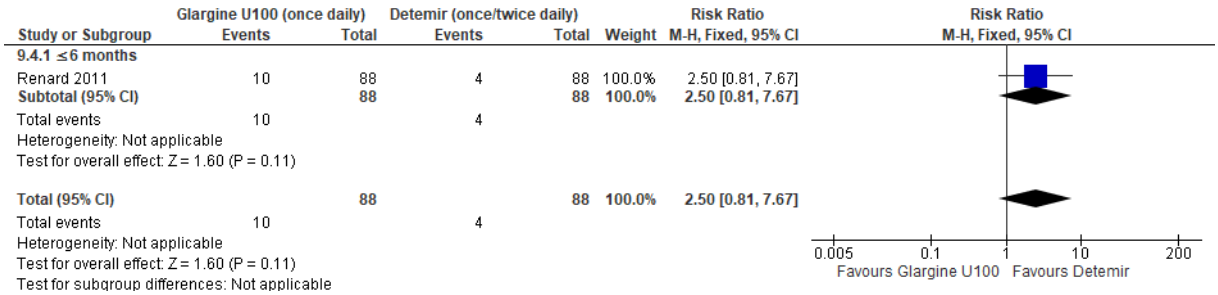


Detemir (Once/twice daily) vs NPH (Once/ twice daily)

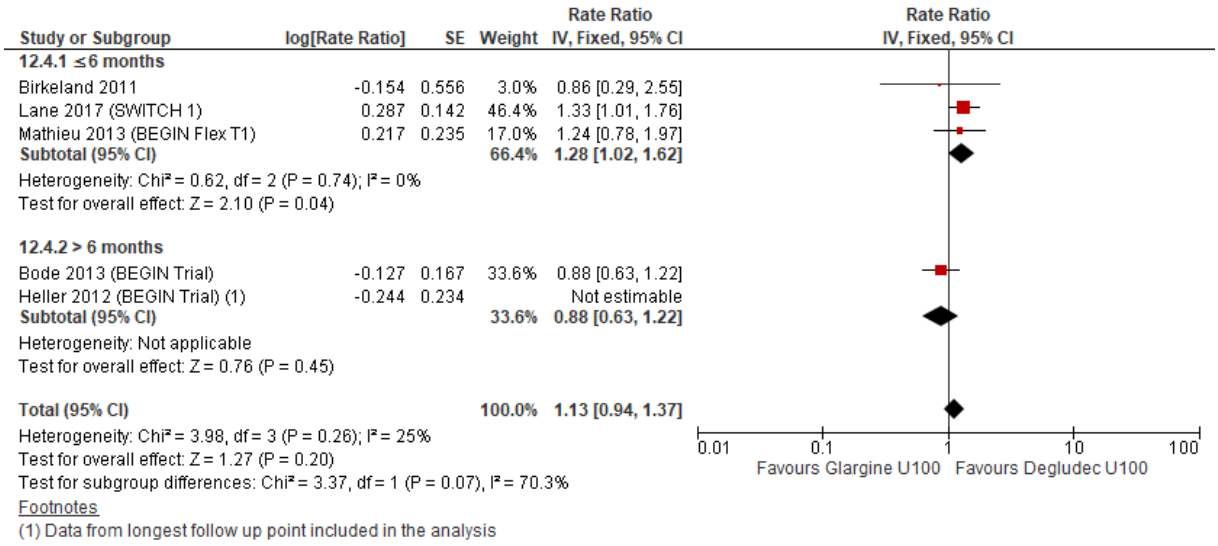


Glargine U100 (Once daily) vs Detemir (Once/Twice daily)





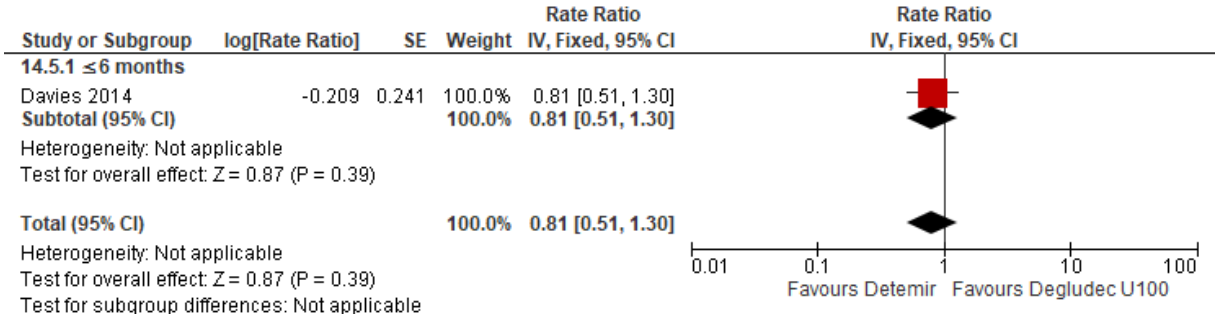
Glargine U100 (Once daily) vs Degludec U100 (Once daily)



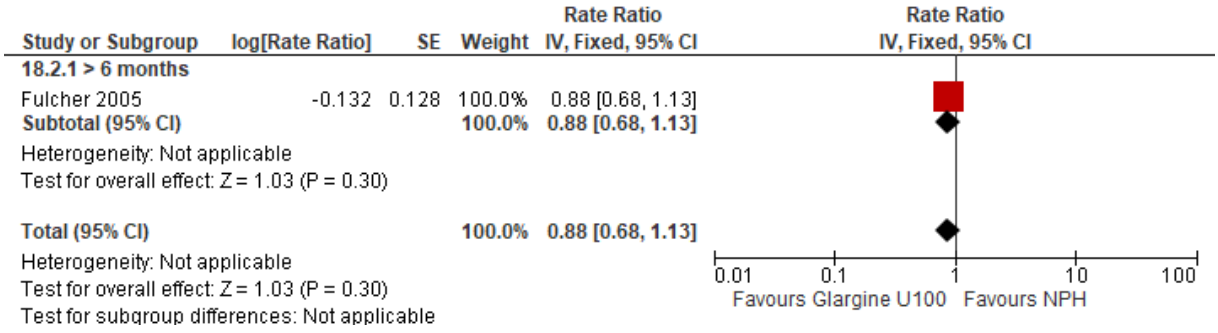
Footnotes

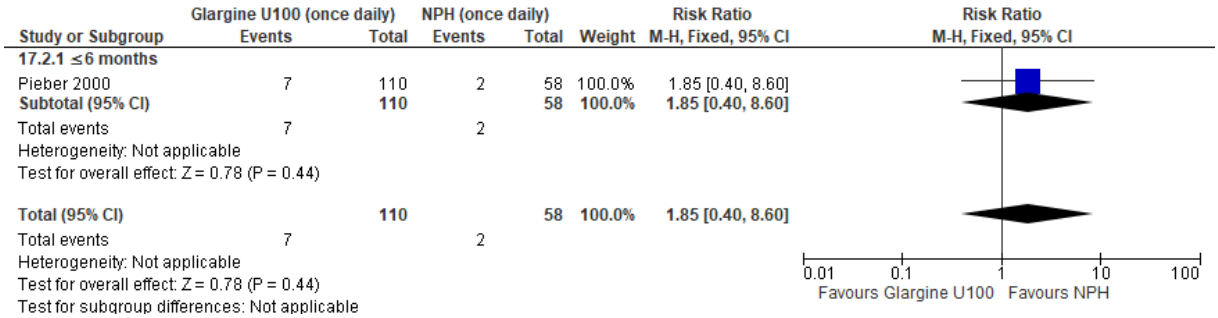
(1) Data from longest follow up point included in the analysis

Detemir (Once daily) vs Degludec U100 (Once daily)

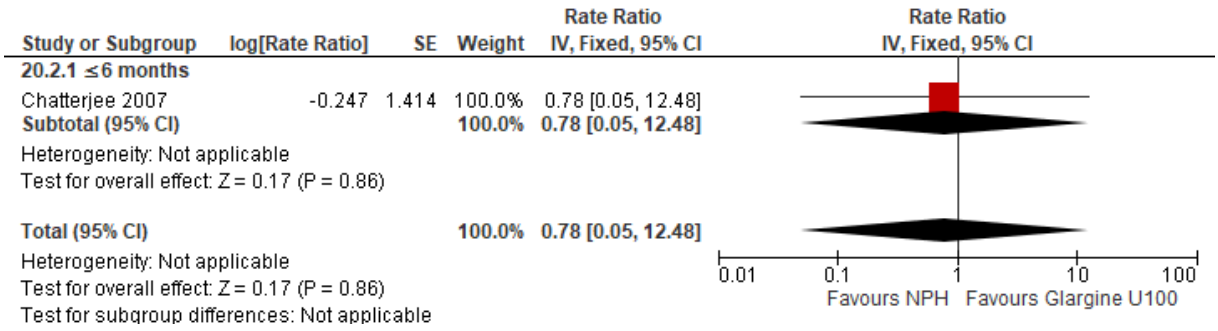


Glargine U100 (Once daily) vs NPH (Once daily)

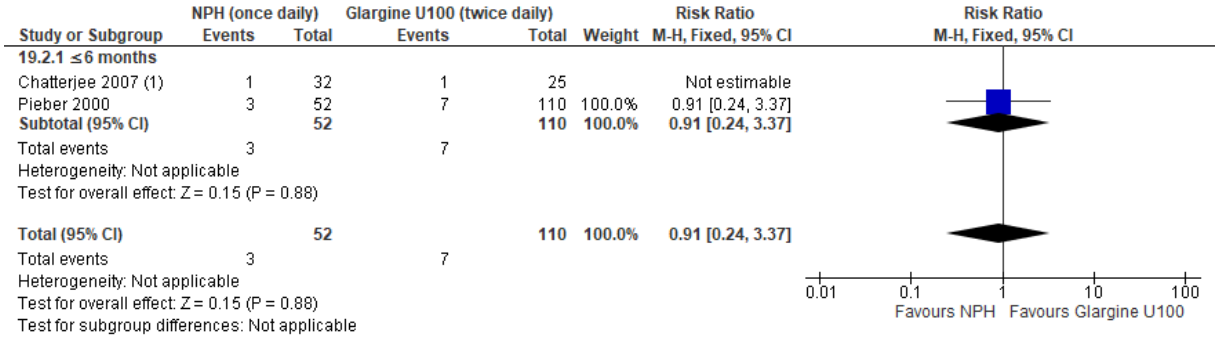




NPH (Twice daily) vs Glargine U100 (Once daily)



Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
20.2.1 ≤6 months				
Chatterjee 2007	-0.247	1.414	100.0%	0.78 [0.05, 12.48]
Subtotal (95% CI)			**100.0%**	**0.78 [0.05, 12.48]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.17 (P = 0.86)				
Total (95% CI)			**100.0%**	**0.78 [0.05, 12.48]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.17 (P = 0.86)				
Test for subgroup differences: Not applicable				

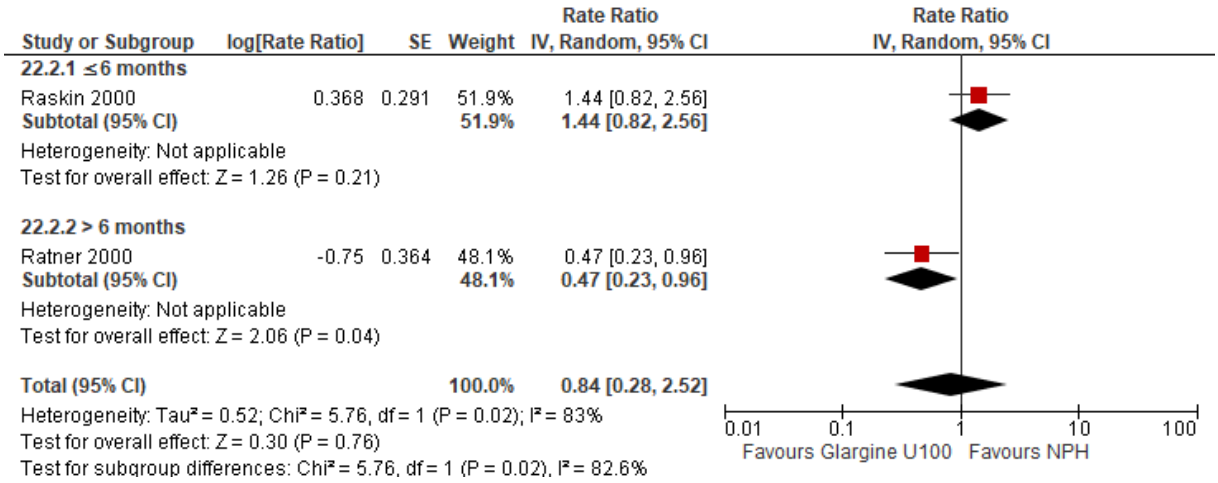


Study or Subgroup	NPH (once daily) Events	NPH (once daily) Total	Glargine U100 (twice daily) Events	Glargine U100 (twice daily) Total	Weight	Risk Ratio M-H, Fixed, 95% CI
19.2.1 ≤6 months						
Chatterjee 2007 (1)	1	32	1	25		Not estimable
Pieber 2000	3	52	7	110	100.0%	0.91 [0.24, 3.37]
Subtotal (95% CI)		**52**		**110**	**100.0%**	**0.91 [0.24, 3.37]**
Total events	3		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
Total (95% CI)		**52**		**110**	**100.0%**	**0.91 [0.24, 3.37]**
Total events	3		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Not applicable						

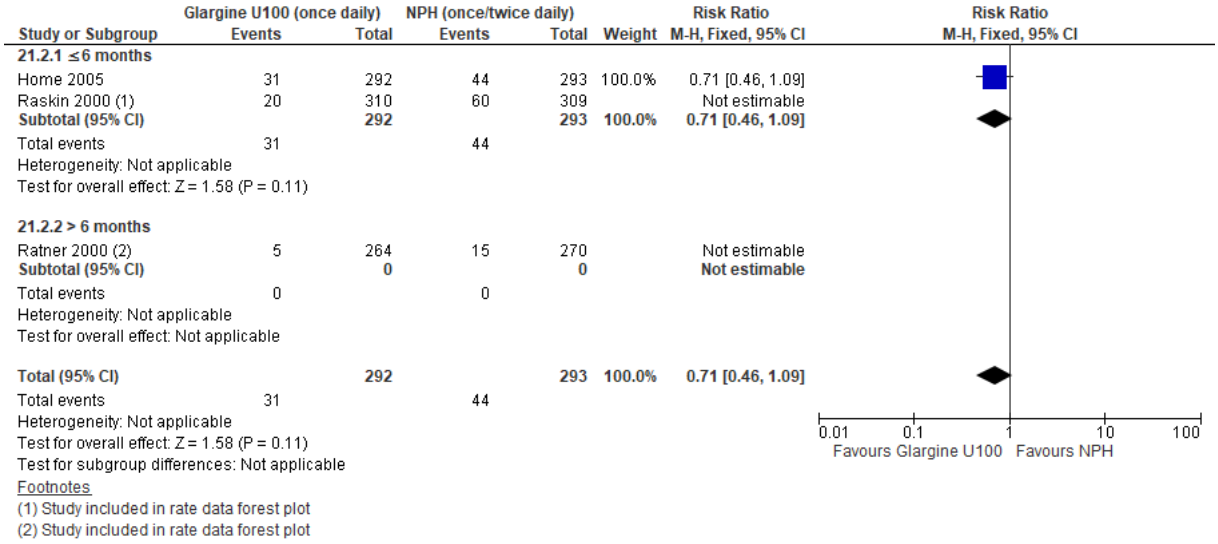
Footnotes

(1) Study included in rate data forest plot

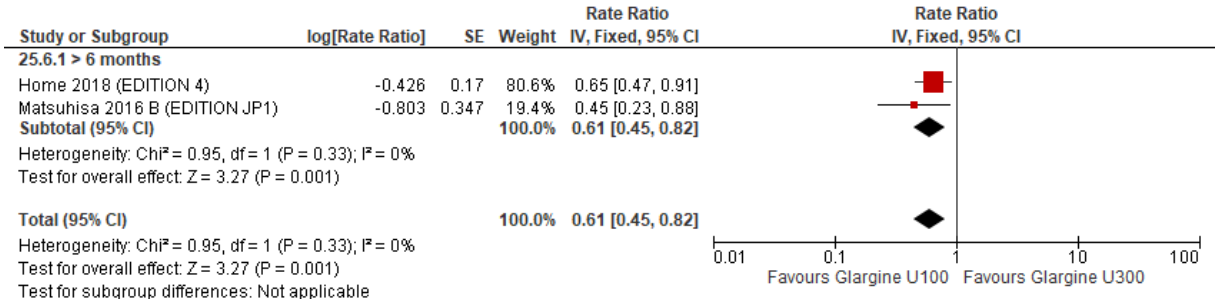
Glargine U100 (Once daily) vs NPH (Once/twice daily)

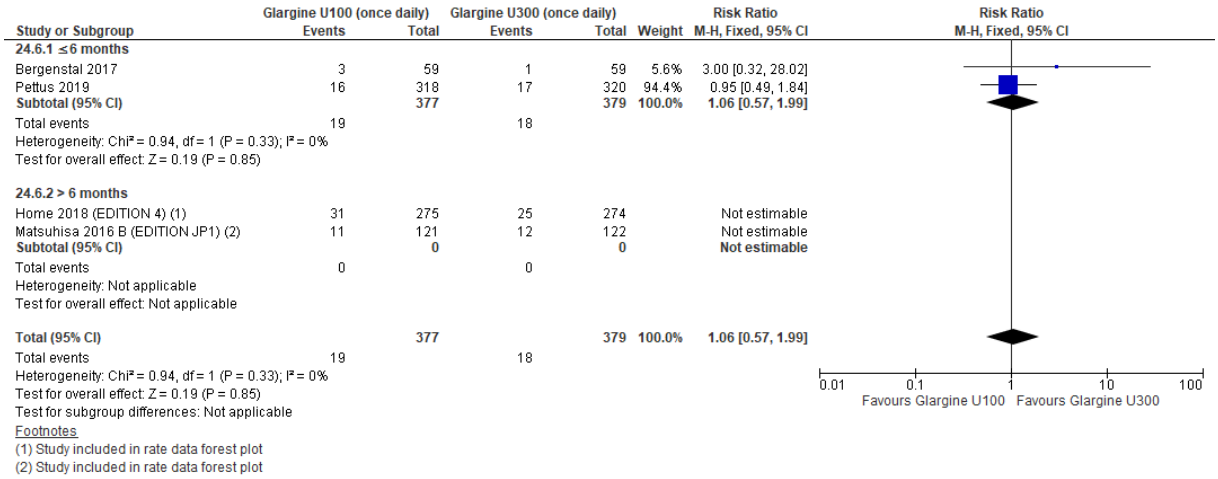


Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
22.2.1 ≤6 months				
Raskin 2000	0.368	0.291	51.9%	1.44 [0.82, 2.56]
Subtotal (95% CI)			**51.9%**	**1.44 [0.82, 2.56]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.26 (P = 0.21)				
22.2.2 > 6 months				
Ratner 2000	-0.75	0.364	48.1%	0.47 [0.23, 0.96]
Subtotal (95% CI)			**48.1%**	**0.47 [0.23, 0.96]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.06 (P = 0.04)				
Total (95% CI)			**100.0%**	**0.84 [0.28, 2.52]**
Heterogeneity: Tau² = 0.52; Chi² = 5.76, df = 1 (P = 0.02); I² = 83%				
Test for overall effect: Z = 0.30 (P = 0.76)				
Test for subgroup differences: Chi² = 5.76, df = 1 (P = 0.02), I² = 82.6%				

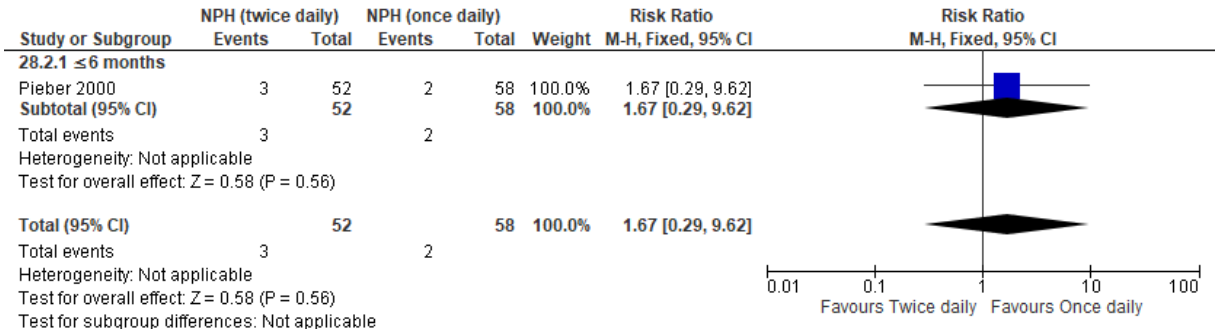


Glargine U100 (Once daily) vs Glargine U300 (Once daily)





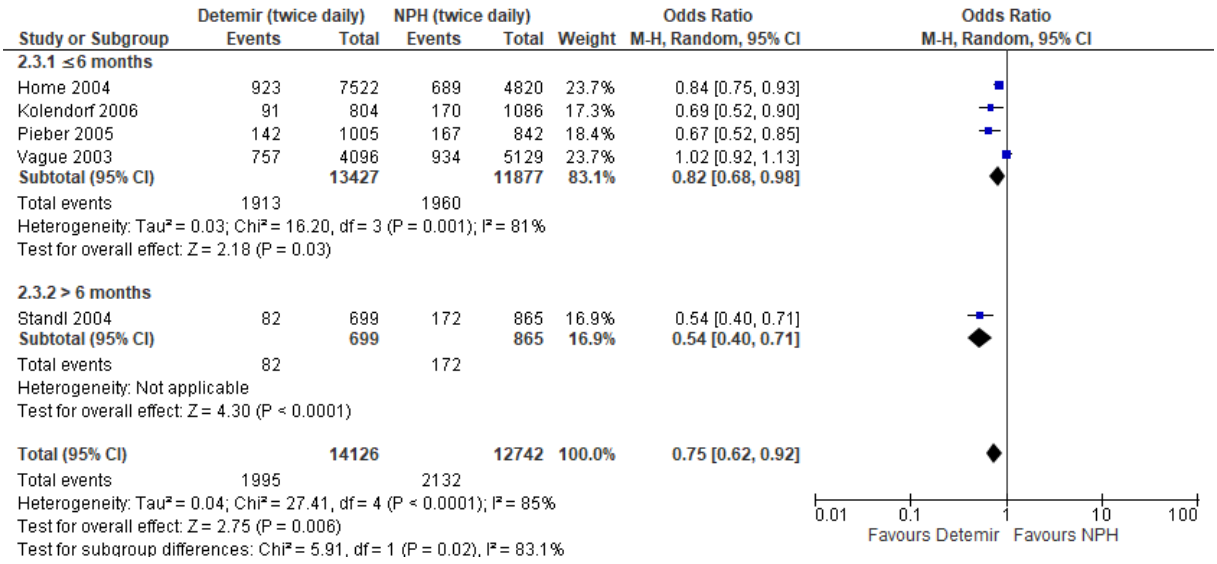
NPH (Twice daily) vs NPH (Once daily)



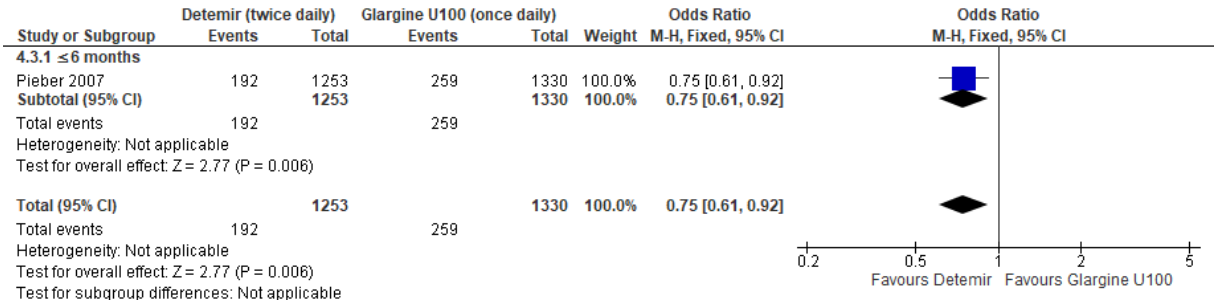
Nocturnal hypoglycaemia

Conditional probability approach was utilised to model nocturnal hypoglycaemia. In this approach, the numerator is the number of nocturnal events and the denominator (total) was the number of all hypoglycaemic events. Data is presented as odds ratio.

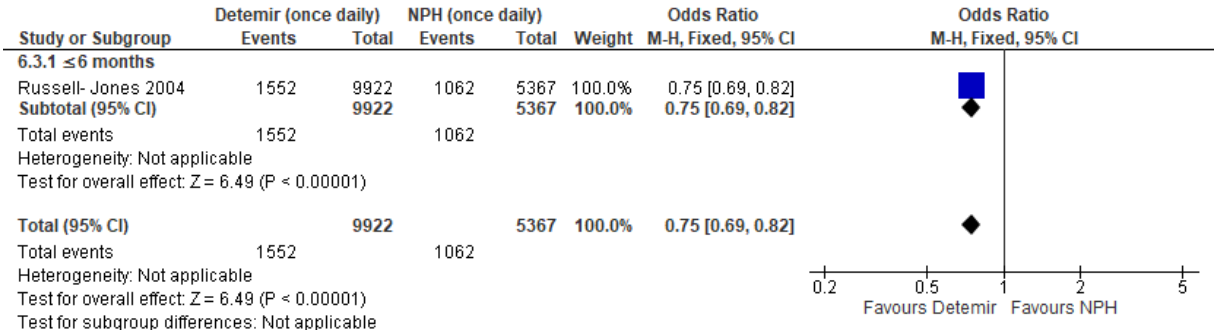
Detemir (Twice daily) vs NPH (Twice daily)



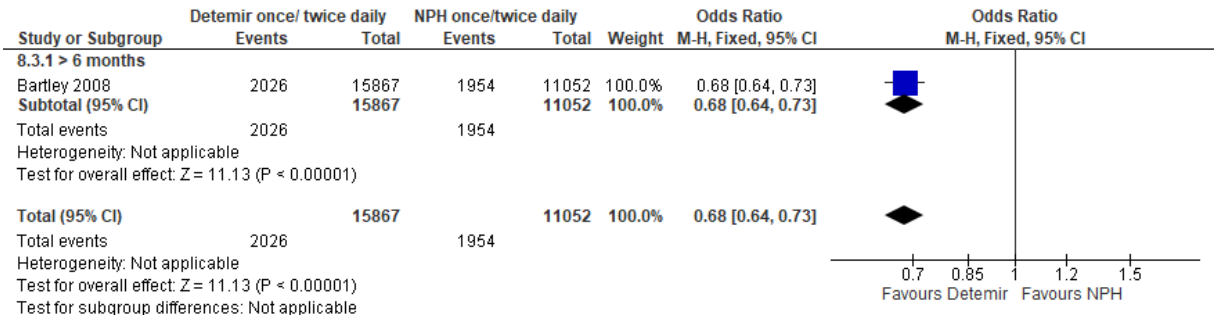
Detemir (Twice daily) vs Glargine U100 (Once daily)



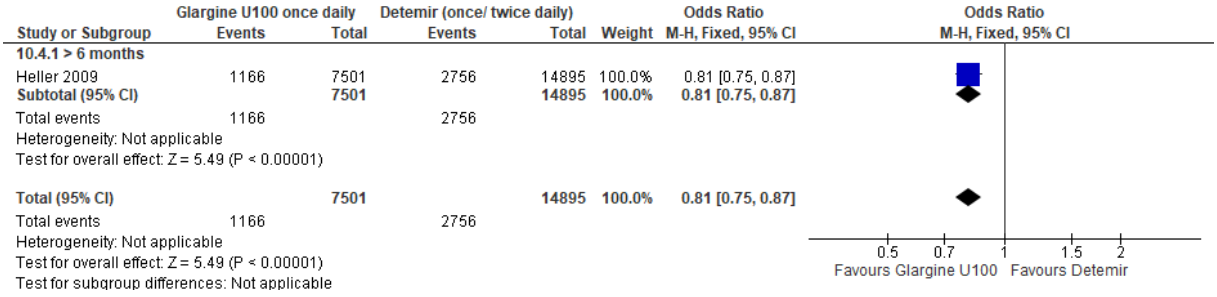
Detemir (Once daily) vs NPH (Once daily)



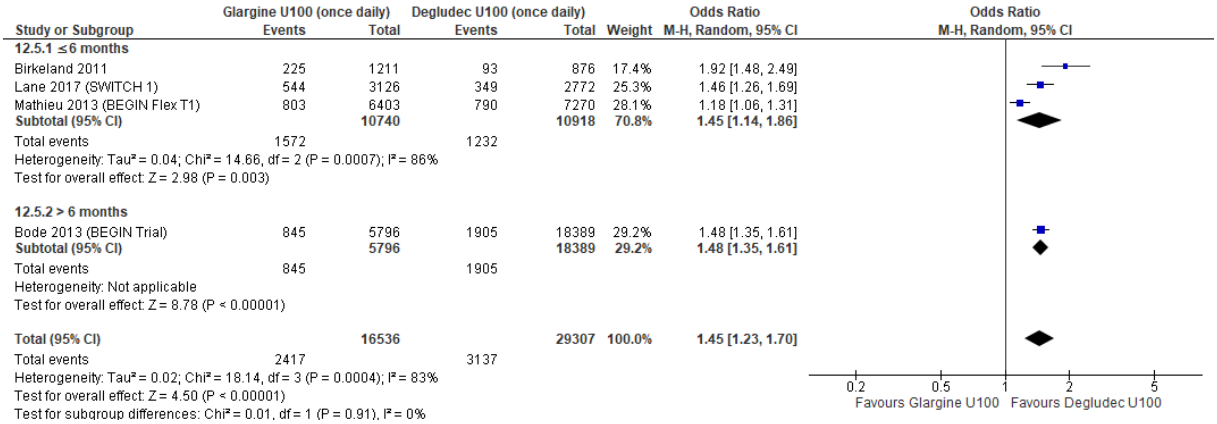
Detemir (Once/twice daily) vs NPH (Once/ twice daily)



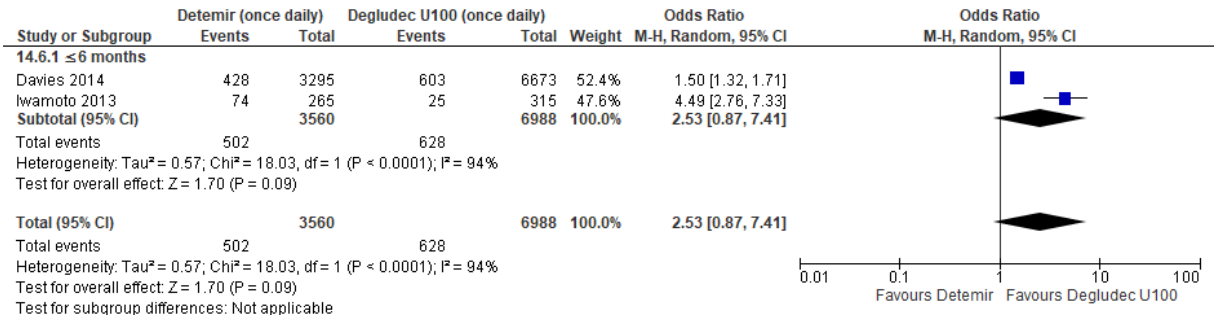
Glargine U100 (Once daily) vs Detemir (Once/Twice daily)



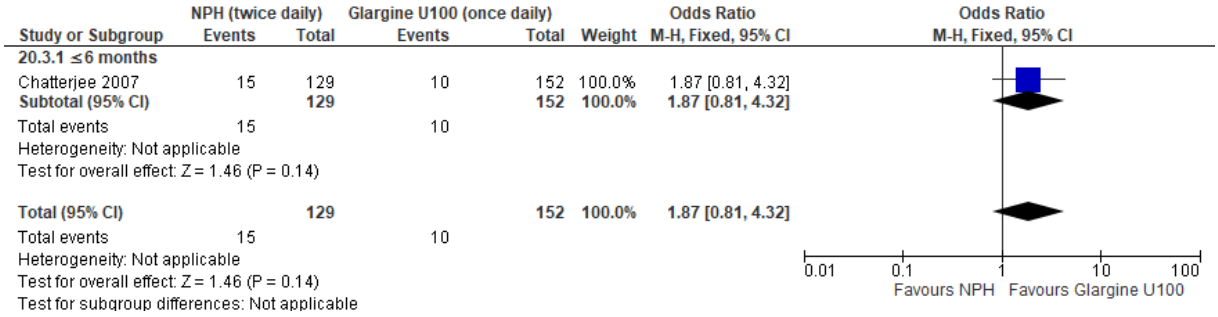
Glargine U100 (Once daily) vs Degludec U100 (Once daily)



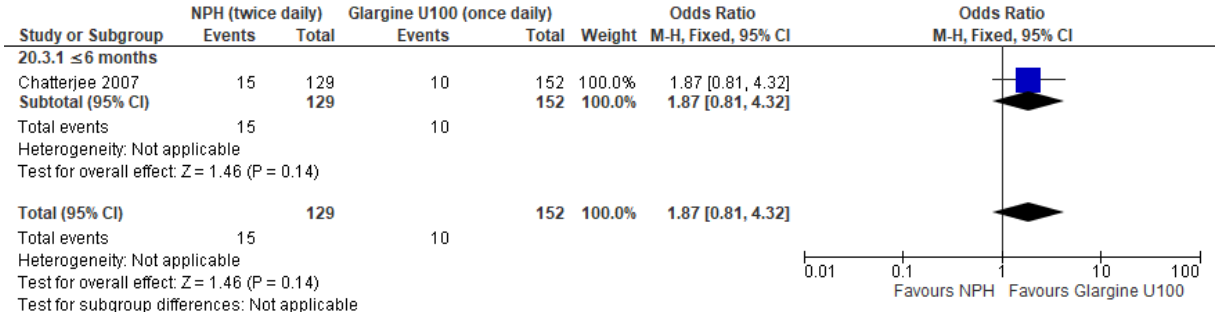
Detemir (Once daily) vs Degludec U100 (Once daily)



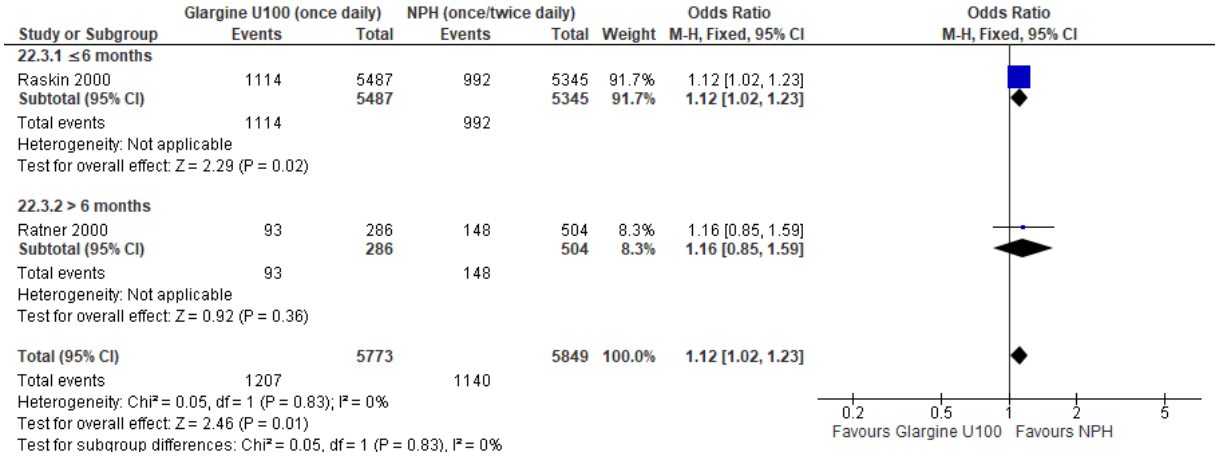
Glargine U100 (Once daily) vs NPH (Once daily)



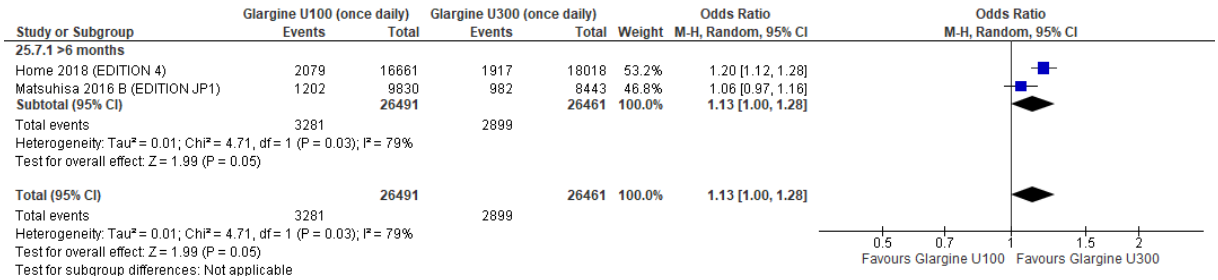
NPH (Twice daily) vs Glargine U100 (Once daily)



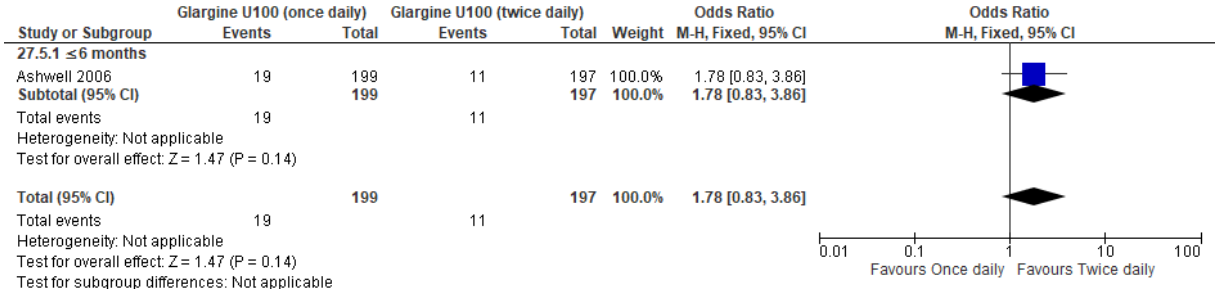
Glargine U100 (Once daily) vs NPH (Once/twice daily)



Glargine U100 (Once daily) vs Glargine U300 (Once daily)



Glargine U100 (Once daily) vs Glargine U100 (Twice daily)


Glargine U100 (once daily)
Glargine U100 (twice daily)
Odds Ratio
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
27.5.1 ≤6 months
Ashwell 2006 19 199 11 197 100.0% 1.78 [0.83, 3.86]
Subtotal (95% CI) 199 197 100.0% 1.78 [0.83, 3.86]
Total events 19 11
Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)
Total (95% CI) 199 197 100.0% 1.78 [0.83, 3.86]
Total events 19 11
Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable
0.01
0.1
1
10
100
Favours Once daily
Favours Twice daily

Appendix H - Additional Data

Glargine U100 vs NPH

Study	Quality of life measured using the Well-Being Enquiry for Diabetics (WED) questionnaire		Glargine U100 once daily	NPH twice (or more) daily	Risk of bias
Bolli 2009	Impact - change (%) 0-6 months	**Median**	-1.4	-4.4	Serious[4]
		IQR[1]	-10, 8	-14, 7	
		P[2]	NS[3]		
	Satisfaction - change (%) 0-6 months	**Median**	0.0	-3	
		IQR[1]	-11, 4	-7,3	
		P[2]	NS	NS	
	General worries - change (%) 0-6 months	**Median**	-1.4	0.0	
		IQR[1]	-7,3	-11, 4	
		P[2]	NS[3]		
	Diabetes related worries	**Median**	-5.7	0.0	
		IQR[1]	-12, 4	-8, 8	
		P[2]	**0.05**		

[1] *IQR: interquartile range*

[2] *p-value*

[3] *no statistical significance*

[4] *Limited information on randomisation and allocation concealment.*

Appendix I - GRADE tables for pairwise data

GRADE tables below highlight findings for outcomes not used in the NMA.

Detemir vs NPH

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Hypoglycaemic episodes - Once/twice daily detemir vs Once/twice daily NPH											
Zachariah 2011	RCT	44	MD: -0.30 (-4.61, 4.01)	-	-	3.59[4]	Serious[5]	NA[6]	No serious	Very serious[7]	Very low
Change in weight (kg)											
6[1]	RCT	1799	MD: -0.86 (-1.29, -0.43)	-	-	5.07[8]	Serious[9]	No serious	No serious	No serious	Moderate
Change in weight (kg) - Once daily detemir vs once daily NPH											
2[2]	RCT	803	MD: -0.79 (-1.49, -0.09)	-	-	1.47[10]	Serious[9]	No serious	No serious	Serious[11]	Low
Change in weight (kg) – Once/ twice daily detemir vs once/twice daily NPH											
Zachariah 2011	RCT	44	MD: -2.39 (-3.66, -1.12)	-	-	1.22[12]	Serious[5]	NA[6]	No serious	Serious[11]	Low
Change in weight (kg) – Twice daily detemir vs Twice daily NPH											
3[3]	RCT	952	MD: -0.63 (-1.05, -0.21)	-	-	5.07[8]	Serious[9]	No serious	No serious	No serious	Moderate
Injection site reactions – Twice daily detemir vs Twice daily NPH											
Vague 2003	RCT	447	RR: 1.46 (0.15, 13.87)	1 per 100 people	1 per 100 people (0 fewer, 10 more)	-	No serious	NA[6]	No serious	Serious[13]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[1] *Russell-Jones 2004, van Golen 2013, Zachariah 2011, Home 2004, Pieber 2005 and Vague 2003*
[2] *Russell-Jones 2004, van Golen 2013*
[3] *Home 2004, Pieber 2005 and Vague 2003*
[4] *MID = 0.5 of the median standard deviation of the comparison group (SD= 7.18).*
[5] *Insufficient information on randomisation process and washout period. Additionally, no test for carryover. Downgrade 1 level for serious risk of bias.*
[6] *Inconsistency not applicable for single study.*
[7] *Downgrade 2 levels for serious imprecision. 95% confidence interval crosses both ends of the estimated MID.*
[8] *Most conservative SD used to calculate MID. MID= 0.5 of the median standard deviation of the comparison group (SD= 10.13).*
[9] *Greater than 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias. Downgrade 1 level for serious risk of bias.*
[10] *Most conservative SD used to calculate MID. MID= 0.5 of the median standard deviation of the comparison group (SD= 2.93).*
[11] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.*
[12] *MID= 0.5 of the median standard deviation of the comparison group (SD= 2.44).*
[13] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.*
**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (%) at follow up – once/twice daily detemir vs once/twice daily NPH											
Bartley 2008	RCT	479	MD: -0.22 (-0.42, -0.02)	-	-	-	Serious[4]	NA[5]	No Serious	No serious	Moderate
Patients achieving HbA1c ≤ 7% - once/twice daily detemir vs once/twice daily NPH											
Bartley 2008	RCT	479	RR: 1.32 (1.00, 1.74)	29 per 100 people	38 per 100 people (29 less, 50 more)	-	Serious[4]	NA[5]	No Serious	No serious	Moderate
Patients achieving HbA1c ≤ 7% in the absence of confirmed hypoglycaemia- once/twice daily detemir vs once/twice daily NPH											
Bartley 2008	RCT	479	RR: 1.66 (1.06, 2.60)	13 per 100 people	22 per 100 people (14 less, 34 more)	-	Serious[4]	NA[5]	No serious	No serious	Moderate
Change in weight (kg)											
2[1]	RCT	794	MD: -1.00 (-1.85, -0.15)	-	-	6.4[6]	Serious[7]	No serious	No serious	No serious	Moderate
Change in weight (kg) - once/twice daily detemir vs once/twice daily NPH											
Bartley 2008	RCT	479	MD: -0.99 (-1.88, -0.10)	-	-	2.34[8]	Serious[4]	NA[5]	No serious	No serious	Moderate
Change in weight (kg) - Twice daily detemir vs twice daily NPH											
De Leeuw 2005	RCT	315	MD: -1.10 (-4.01, 1.81)	-	-	6.4[6]	Very serious[9]	NA[5]	No serious	No serious	Low
Injection site reactions - Twice daily detemir vs twice daily NPH											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2[2]	RCT	603	RR: 3.70 (0.86, 15.83)	1 per 100 people	3 per 100 people (1 less, 14 more)	-	Very serious[10]	No serious	No serious	Serious[11]	Very low
Adverse events											
2[3]	RCT	783	RR: 1.03 (0.36, 2.92)	12 per 100 people	12 per 100 people (4 less, 35 more)	-	Serious[7]	Very serious[12]	No serious	Serious[11]	Very low
Adverse events - once/twice daily detemir vs once/twice daily NPH											
Bartley 2008	RCT	495	RR: 0.64 (0.40, 1.01)	17 per 100 people	11 per 100 people (7 less, 17 more)	-	Serious[4]	NA[5]	No serious	Serious[11]	Low
Adverse events - Twice daily detemir vs twice daily NPH											
Standl 2004	RCT	288	RR: 1.85 (0.82, 4.15)	6 per 100 people	11 per 100 people (5 less, 25 more)	-	Very serious[13]	NA[5]	No serious	Serious[11]	Very low
Serious AEs											
2[1]	RCT	810	RR: 0.64 (0.32, 1.29)	5 per 100 people	3 per 100 people (2 less, 6 more)	-	Serious[7]	No serious	No serious	Serious[11]	Low
Serious AEs- once/twice daily detemir vs once/twice daily NPH											
Bartley 2009	RCT	495	RR: 0.63 (0.29, 1.36)	7 per 100 people	4 per 100 people (2 less, 9 more)	-	Serious[14]	NA[5]	No serious	Serious[11]	Low
Serious AEs- Twice daily detemir vs twice daily NPH											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
De Leeuw 2005	RCT	315	RR: 0.69 (0.12, 4.05)	2 per 100 people	1 per 100 people (0 less, 3 more)	-	Very serious[9]	NA[5]	No serious	Serious[11]	Very low

[1] *Bartley 2009 and De Leeuw 2005*

[2] *De Leeuw 2005 and Standl 2004*

[3] *Bartley 2009 and Standl 2004*

[4] *More patients withdrew from the detemir arm than the NPH arm due to adverse events. Downgrade 1 level for serious risk of bias.*

[5] *Inconsistency not applicable for single study.*

[6] *Most conservative SD used to calculate MID. MID = 0.5 of the median standard deviation of the comparison group (SD= 12.8).*

[7] *Greater than 33.3% of the weight in a meta-analysis came from studies at moderate and high risk of bias. Downgrade 1 level for serious risk of bias.*

[8] *MID = 0.5 of the median standard deviation of the comparison group (SD= 4.67).*

[9] *Limited information on randomisation and allocation concealment. Additionally, initial treatment phase was followed by an extension phase which was not considered randomised. Downgrade 2 levels for very serious risk of bias.*

[10] *Greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias. Downgrade 2 levels for very serious risk of bias.*

[11] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.*

[12] *I^2 was greater than 66.7%. Downgrade 2 levels for very serious inconsistency.*

[13] *Limited information on randomisation and allocation concealment. Additionally, initial treatment phase was followed by an extension phase which was not considered randomised. Open label study design could have introduced bias for subjective outcomes. Downgrade 2 levels for very serious risk of bias.*

[14] *Open label study design could have introduced bias for subjective outcomes. Downgrade 1 level for serious risk of bias.*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Detemir vs Glargine U100

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (%) at follow up – Det: Twice daily vs IGlar: Once daily											
Pieber 2007	RCT	293	MD: -0.03 (-0.26, 0.20)	-	-	-	No serious	NA[1]	No serious	No serious	High
Change in weight (kg)- Det: Twice daily vsIGlar: Once daily											
Pieber 2007	RCT	293	MD: -0.44 (-1.15, 0.27)	-	-	1.51[2]	No serious	NA[1]	No serious	No serious	High
Adverse events - Det: Once/twice daily vs IGlar: Once daily											
Renard 2011	RCT	80	RR: 0.39 (0.04, 4.12)	6 per 100 people	2 per 100 people (0 less, 24 more)	-	Very serious[3]	NA[1]	No serious	Serious[4]	Very low
Serious AEs											
2[5]	RCT	373	RR: 0.53 (0.18, 1.58)	4 per 100 people	2 per 100 people (1 less, 7 more)	-	Very serious[6]	No serious	No serious	Serious[4]	Very low
Serious AEs - Det: Twice daily vs IGlar: Once daily											
Pieber 2007	RCT	293	RR: 0.25 (0.03, 2.20)	3 per 100 people	1 per 100 people (0 less, 6 more)	-	Serious[7]	NA[1]	No serious	Serious[4]	Low
Serious AEs - Det: Once/twice daily vs IGlar: Once daily											
Renard 2011	RCT	80	RR: 0.78 (0.21, 2.89)	11 per 100 people	9 per 100 people (2 less, 33 more)	-	Very serious[3]	NA[1]	No serious	Serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[1] *Inconsistency not applicable for single study.*

[2] *MID = 0.5 of the median standard deviation of the comparison group (SD= 3.02).*

[3] *Limited information about randomisation and allocation concealment. Imbalances in the number of participants in each arm of the trial, washout period not specified and no evidence of statistical test for carryover. Downgrade 2 levels for very serious risk of bias.*

[4] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.*

[5] *Pieber 2007 and Renard 2011*

[6] *Greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias. Downgrade 2 levels for very serious risk of bias.*

[7] *Open label trial design could have introduced bias for subjective outcomes. Downgrade 1 level for serious risk of bias.*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Patients achieving HbA1c ≤ 7% – Det: Once/twice daily vs IGlar: Once daily											
Heller 2009	RCT	443	RR: 1.08 (0.81, 1.45)	31 per 100 people	33 per 100 people (25 less, 44 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Change in weight (kg) – Det: Once/twice daily vs IGlar: Once daily											
Heller 2009	RCT	443	MD: -0.06 (-0.84, 0.72)	-	-	1.96[4]	Serious[1]	NA[2]	No serious	No serious	Moderate
Injection site reactions – Det: Once/twice daily vs IGlar: Once daily											
Heller 2009	RCT	443	RR: 5.78 (1.38, 24.12)	1 per 100 people	8 per 100 people (2 less, 34 more)	-	Serious[1]	NA[2]	No serious	No serious	Moderate
Adverse events – Det: Once/twice daily vs IGlar: Once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Heller 2009	RCT	443	RR: 1.03 (0.97, 1.10)	90 per 100 people	92 per 100 people (87 less, 99 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Serious adverse events – Det: Once/twice daily vs IGlar: Once daily											
Heller 2009	RCT	443	RR: 5.78 (0.76, 44.02)	1 per 100 people	4 per 100 people (1 less, 31 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low

[1] *Deviation from protocol (participants were assigned to once daily glargine U100 but physicians chose to split the glargine dose). Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

[3] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.*

[4] *MID = 0.5 of the median standard deviation of the comparison group (SD= 3.92).*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Degludec U100 vs Glargine U100

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in weight (kg) – Once daily											
3[1]	RCT	948	MD: -0.40 (-0.88, 0.07)	-	-	1.85[2]	No serious	Serious[3]	No serious	No serious	Moderate
Injection site reactions - Once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2[4]	RCT	378	RR: 0.73 (0.17, 3.22)	2 per 100 people	2 per 100 people (0 less, 7 more)	-	No serious	No serious	No serious	Serious[5]	Moderate
Adverse events – Once daily											
1[6]	RCT	326	RR: 1.25 (0.78, 2.01)	16 per 100 people	20 per 100 people (13 less, 32 more)	-	No serious	No serious	No serious	Serious[5]	Moderate
Serious AEs – Once daily											
3[7]	RCT	496	RR: 0.82 (0.25, 2.64)	2 per 100 people	2 per 100 people (1 less, 6 more)	-	No serious	No serious	No serious	Serious[5]	Moderate
QoL – Change in SF36 physical component scores – Once daily											
Home 2012	RCT	118	MD: 0.67 (-2.31, 3.65)	-	-	4.11[8]	Serious[9]	NA[10]	No serious	No serious	Moderate
QoL – Change in SF36 mental component scores – Once daily											
Home 2012	RCT	118	MD: 3.01 (0.31, 5.71)	-	-	3.73[11]	Serious[9]	NA[10]	No serious	Serious[12]	Low

[1] *Birkeland 2011, Lane 2017 and Mathieu 2013*
[2] *Most conservative SD used to calculate MID. MID = 0.5 of the median standard deviation of the comparison group (SD= 3.7).*
[3] *I^2 was between 33.3% and 66.7%. Downgrade 1 level for serious inconsistency.*
[4] *Heise 2012 and Mathieu 2013*
[5] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.*
[6] *Mathieu 2013*
[7] *Birkeland 2011, Heise 2012 and Mathieu 2013*
[8] *MID = 0.5 of the median standard deviation of the comparison group (SD= 8.22).*
[9] *Open label trial design could have introduced bias for subjective outcomes. Downgrade 1 level for serious risk of bias.*

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[10] *Inconsistency not applicable for single study.*
[11] *MID = 0.5 of the median standard deviation of the comparison group (SD= 7.45).*
[12] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.*
**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Patients achieving HbA1c target (<7%, <53 mmol/mol) – once daily											
Heller 2012	RCT	629	RR: 0.93 (0.75, 1.15)	43 per 100 people	40 per 100 people (32 less, 49 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Change in weight (kg) – Once daily											
Heller 2012	RCT	629	MD: 0.20 (-0.51, 0.91)	-	-	1.9[4]	No serious	NA[1]	No serious	No serious	High
Injection site reaction– Once daily											
1[3]	RCT	629	RR: 0.51 (0.22, 1.15)	6 per 100 people	3 per 100 people (1 less, 7 more)	-	Serious[5]	NA[1]	No serious	Serious[2]	Low
Adverse events – Once daily											
2[6]	RCT	1,230	RR: 0.94 (0.64, 1.40)	36 per 100 people	35 per 100 people (23 less, 50 more)	-	Serious[7]	No serious	No serious	Serious[2]	Low
Serious AEs - Once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2[6]	RCT	1,230	RR: 0.83 (0.59, 1.17)	10 per 100 people	9 per 100 people (6 less, 12 more)	-	Serious[7]	No serious	No serious	Serious[2]	Low

[1] *Inconsistency not applicable for single study.*
[2] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.*
[3] *BEGIN Trail (Bode 2013 and Heller 2012). Only data from Bode 2013 was included as this study reported data from 104 weeks follow up of the BEGIN Trial.*
[4] MID = 0.5 of the median standard deviation of the comparison group (SD= 3.8)
[5] *Study (Bode 2013) is an extension of heller 2012. Unclear how patients were recruited onto the extension trial. Downgrade 1 level for serious risk of bias.*
[6] *BEGIN Trial (Bode 2013) and Lane 2017 (SWTICH Trial).*
[7] *Greater than 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias. Downgrade 1 level for serious risk of bias.*
**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Degludec U200 vs Glargine U300

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Adverse events – Once daily											
Heise 2017	RCT	60	RR: 1.00 (0.51, 1.97)	22 per 100 people	22 per 100 people (11 less, 43 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Serious AEs– Once daily											
Heise 2017	RCT	60	RR not estimable due to zero event in both arms				Serious[1]	NA[2]	No serious	Very serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[1] *Limited information about randomisation, allocation concealment and baseline characteristics. Downgrade 1 level for serious risk of bias.*
[2] *Inconsistency not applicable for single study.*
[3] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.*
[4] *Effect size could not be calculated. Downgrade 2 levels due to very serious imprecision.*
**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Degludec vs Glargine (conc. not defined)

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (%) at follow up – once daily											
Iga 2017	RCT	40	MD: -0.10 (-0.63, 0.43)	-	-	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Percentage of time in target glucose range (70 and 140 mg/dL (3.9–7.8 mmol/L)) – once daily											
Iga 2017	RCT	40	MD: 1.20 (-11.22, 13.62)	-	-	-	Serious[1]	NA[2]	Serious[3]	Very serious[5]	Very low
Time in hypoglycaemia (<70 mg/dL) during 24 hours (minutes) – IDeg: once daily, IGlar: twice daily											
Onda 2017	RCT	26	MD: 47.70 (-118.12, 213.52)	-	-	107.85[6]	Very serious[7]	NA[2]	Serious[3]	Very serious[8]	Very low
Percentage of time spent in hypoglycaemia – once daily											
Iga 2017	RCT	40	MD: 1.20 (-3.74, 6.14)	-	-	3.25[9]	Serious[1]	NA[2]	Serious[3]	Very serious[8]	Very low
Percentage of time spent in nocturnal hypoglycaemia – once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Iga 2017	RCT	40	MD: 4.50 (-12.90, 21.90)	-	-	12.65[10]	Serious[1]	NA[2]	Serious[3]	Very serious[8]	Very low

[1] *Study did not specify washout period and no information provided about statistical test for carry-over. Downgrade 1 level for serious risk of bias.*
[2] *Inconsistency not applicable for single study.*
[3] *Study did not specify concentration of degludec and glargine. Downgrade 1 level for serious indirectness.*
[4] *Downgrade 1 level for serious imprecision. 95% CI crosses one end of the defined MD (-0.5, 0.5)*
[5] *95% CI crosses both ends of the defined MD (-5, 5). Downgrade 2 levels for serious imprecision.*
[6] *MID = 0.5 of the median standard deviation of the comparison group (SD= 215.7)*
[7] *Limited information on randomisation and allocation concealment. No information about statistical test for carryover. Downgrade 2 levels for very serious risk of bias.*
[8] *95% confidence interval crosses both ends of the estimated MID. Downgrade 2 levels for very serious imprecision.*
[9] *MID = 0.5 of the median standard deviation of the comparison group (SD= 6.5)*
[10] *MID = 0.5 of the median standard deviation of the comparison group (SD= 25.3).*

Degludec U100 vs Detemir

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Participants achieving HbA1c <7% - once daily											
Davies 2014	RCT	453	RR: 1.10 (0.86, 1.41)	37 per 100 people	41 per 100 people (32 less, 53 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Change in weight (kg) – once daily											
Davies 2018	RCT	453	MD: 1.10 (0.55, 1.65)	-	-	1.24[2]	No serious	NA[1]	No serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Injection site reactions- once daily											
Davies 2018	RCT	453	RR: 2.02 (0.58, 7.05)	2 per 100 people	4 per 100 people (1 less, 14 more)	-	Serious[4]	NA[1]	No serious	Serious[2]	Low
Adverse events– once daily											
2[1]	RCT	518	RR: 1.15 (0.78, 1.70)	16 per 100 people	18 per 100 people (12 less, 18 more)	-	Serious[6]	No serious	No serious	Serious[2]	Low
Serious AEs- once daily											
Davies 2018	RCT	453	RR: 1.45 (0.67, 3.17)	25 per 100 people	36 per 100 people (17, 43)	-	Serious[4]	NA[1]	No serious	Serious[2]	Low

[1] *Inconsistency not applicable for single study.*

[2] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[3] *MID = 0.5 of the median standard deviation of the comparison group (SD= 2.47).*

[4] *Open label study design could have influenced subjective outcomes in study. Downgrade 1 level for serious risk of bias.*

[5] *Davies 2014, Iwamoto 2013*

[6] *Greater than 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias. Downgrade 1 level for serious risk of bias.*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Glargine U100 vs NPH

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c (%)- Glargine: once daily vs NPH: 4 x daily- bedtime											
Rossetti 2003	RCT	34	MD: -0.50 (-0.89, -0.11)	-	-	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Change in HbA1c (%)- Glargine: once daily vs NPH: 4 x daily- dinnertime											
Rossetti 2003	RCT	34	MD: -0.51 (-0.90, -0.12)	-	-	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Frequency of mild hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily- bedtime											
Rossetti 2003	RCT	34	MD: -4.50 (-7.60, -1.40)	-	-	2.68[5]	Serious[1]	NA[2]	Serious[3]	Serious[6]	Very low
Frequency of mild hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily- dinnertime											
Rossetti 2003	RCT	34	MD: -4.10 (-7.09, -1.11)	-	-	2.68[5]	Serious[1]	NA[2]	Serious[3]	Serious[6]	Very low
Frequency of nocturnal hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily- bedtime											
Rossetti 2003	RCT	34	MD: -1.60 (-2.47, -0.73)	-	-	0.83[7]	Serious[1]	NA[2]	Serious[3]	Serious[6]	Very low
Frequency of nocturnal hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily- dinnertime											
Rossetti 2003	RCT	34	MD: -1.90 (-2.78, -1.02)	-	-	0.83[7]	Serious[1]	NA[2]	Serious[3]	Serious[6]	Very low
Change in weight (kg) - Glargine: once daily vs NPH: twice daily											
Chatterjee 2007	RCT	120	MD: -0.24 (-4.97, 4.49)	-	-	6.61[8]	Serious[9]	NA[2]	No serious	No serious	Moderate
Injection site reactions - Glargine: once daily vs NPH: once or twice daily											
2[11]	RCT	739	RR: 1.14 (0.70, 1.85)	8 per 100 people	9 per 100 people (5	-	Serious[11]	No serious	No serious	Serious[12]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					less, 13 more)						
Adverse events- Glargine: once daily vs NPH: once or twice daily											
Raskin 2000	RCT	103	RR: 1.31 (0.91, 1.89)	17 per 100 people	22 per 100 people (15 less, 32 more)	-	Serious[13]	NA[2]	No serious	Serious[13]	Low

[1] *Study did not provide information of allocation concealment and randomisation. Additionally, method of analysis to estimate the effect of assignment to intervention not specified. Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

[3] *Participants received once daily glargine U100 but 4-times daily NPH which does not match review protocol. Downgrade 1 level for serious indirectness.*

[4] *95% CI crosses one end of the defined MID (-0.5, 0.5). Downgrade 1 level for imprecision.*

[5] *MID = 0.5 of the median standard deviation of the comparison group (SD= 5.36).*

[6] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.*

[7] *MID = 0.5 of the median standard deviation of the comparison group (SD= 1.65). .*

[8] *MID = 0.5 of the median standard deviation of the comparison group (SD= 13.21).*

[9] *Baseline characteristics not reported for each arm, no washout period, and no information about statistical test for carry-over. Downgrade 1 level for serious risk of bias.*

[10] *Pieber 2005 and Raskin 2000*

[11] *Greater than 33.3% of the weight in meta-analysis from studies with moderate risk of bias. Downgrade 1 level for serious risk of bias.*

[12] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[13] *Open label trial could have influenced subjective outcomes in study. Downgrade 1 level for serious risk of bias.*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in hypoglycaemia (episodes/ patient/ month) – Glargine: once daily vs NPH: twice (or more)											
Bolli 2009	RCT	175	MD: 0.05 (-1.47, 1.57)	-	-	2.58[1]	Serious[2]	NA[3]	Serious[4]	No serious	Low
Change in severe hypoglycaemia (episodes/ patient/ month) – Glargine: once daily vs NPH: twice (or more)											
Bolli 2009	RCT	175	MD: 0.00 (-0.60, 0.60)	-	-	1.03[5]	Serious[2]	NA[3]	Serious[4]	No serious	Low
Change in severe nocturnal hypoglycaemia (episodes/ patient/ month) – Glargine: once daily vs NPH: twice (or more)											
Bolli 2009	RCT	175	MD: -0.09 (-0.28, 0.10)	-	-	0.34[6]	Serious[2]	NA[3]	Serious[4]	No serious	Low
Frequency of hypoglycaemia (episodes/ patient/ month) - Glargine: once daily vs NPH: 4 x daily											
Porcellati 2004	RCT	121	MD: -4.00 (-5.98, -2.04)	-	-	3.1[7]	No serious	NA[3]	Serious[8]	Serious[9]	Low
Frequency of nocturnal hypoglycaemia (episodes/ patient / month) – Glargine: once daily vs NPH: 4 x daily											
Porcellati 2004	RCT	121	MD: -2.00 (-2.71, -1.29)	-	-	1.16[10]	No serious	NA[3]	Serious[8]	No serious	Moderate
Injection site reactions											
3[11]	RCT	1244	RR: 1.19 (0.81, 1.77)	7 per 100 people	8 per 100 people (5 less,13 more)	-	Serious[12]	Serious[13]	No serious	Serious[14]	Very low
Injection site reactions – once daily											
Fulcher 2005	RCT	125	RR: 0.73 (0.24, 2.16)	8 per 100 people	6 per 100 people (2 less, 18 more)	-	Very serious[15]	NA[3]	No serious	Serious[14]	Very low
Injection site reactions - Glargine: once daily vs NPH: once or twice daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2[2]	RCT	1119	RR: 1.29 (0.84, 1.97)	6 per 100 people	8 per 100 people (5 less,12 more)	-	Serious[16]	Serious[13]	No serious	Serious[14]	Very low
Adverse events											
3[17]	RCT	885	RR: 1.00 (0.83, 1.20)	22 per 100 people	22 per 100 people (18 less, 26 more)	-	Serious[12]	No serious	No serious	Serious[14]	Low
Adverse events – Once daily											
Fulcher 2005	RCT	125	RR: 1.03 (0.92, 1.16)	89 per 100 people	92 per 100 people (82 less, 103 more)	-	Very serious[15]	NA[3]	No serious	Serious[14]	Very low
Adverse events – Glargine: once daily vs NPH: once or twice daily											
Home 2005	RCT	585	RR: 0.95 (0.63, 1.45)	13 per 100 people	13 per 100 people (8 less, 19 more)	-	No serious	NA[3]	No serious	Serious[14]	Moderate
Adverse events- Glargine: once daily, NPH: twice (or more)											
Bolli 2009	RCT	175	RR: 1.06 (0.07, 16.66)	1 per 100 people	1 per 100 people (0 less, 19 more)	-	Serious[2]	NA[3]	Serious[4]	Serious[14]	Very low
Serious AES											
3[18]	RCT	834	RR: 1.43 (0.47, 4.41)	1 per 100 people	2 per 100 people (1 less, 5 more)	-	Serious[12]	No serious	No serious	Serious[14]	Low
Serious AES – Once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Fulcher 2005	RCT	125	RR: 1.69 (0.42, 6.78)	5 per 100 people	8 per 100 people (2 less, 32 more)	-	Very serious[15]	NA[3]	No serious	Serious[14]	Very low
Serious AEs- Glargine: once daily vs NPH: twice (or more)											
Bolli 2009	RCT	175	RR: 1.06 (0.07, 16.66)	1 per 100 people	1 per 100 people (0 less, 19 more)	-	Serious[2]	NA[3]	Serious[4]	Serious[14]	Very low
Serious AEs- Glargine: once daily, NPH: once or twice											
Ratner 2000	RCT	534	RR: 1.02 (0.06, 16.27)	0 per 100 people	Not estimable because of very low/ zero events	-	Serious[19]	NA[3]	No serious	Serious[14]	Low
QoL – DTSQ- change in treatment satisfaction from baseline – Glargine: once daily vs NPH: once or more than once (higher score indicating greater satisfaction)											
Witthaus 2001	RCT	517	MD: 1.83 (0.82, 2.84)	-	-	2.93[20]	Serious[21]	NA[3]	No serious	No serious	Moderate
QoL – DTSQ- change in perceived frequency of hyperglycaemia from baseline – Glargine: once daily vs NPH: once or more than once (Lower score indicates greater satisfaction)											
Witthaus 2001	RCT	517	MD: -0.25 (-0.49, -0.01)	-	-	0.70[22]	Serious[21]	NA[3]	No serious	No serious	Moderate
QoL – DTSQ- change in perceived frequency of hypoglycaemia from baseline – Glargine: once daily vs NPH: once or more than once (Lower score indicates greater satisfaction)											
Witthaus 2001	RCT	517	MD: -0.05 (-0.27, 0.17)	-	-	0.64[23]	Serious[21]	NA[3]	No serious	No serious	Moderate
QoL – W-BQ22- change in general wellbeing from baseline – Glargine: once daily vs NPH: once or more than once (Higher score indicates greater wellbeing)											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Witthaus 2001	RCT	517	MD: -0.35 (-1.50, 0.80)	-	-	3.34[24]	Serious[21]	NA[3]	No serious	No serious	Moderate
QoL – W-BQ22- change in depression from baseline – Glargine: once daily vs NPH: once or more than once (Lower score indicates greater wellbeing)											
Witthaus 2001	RCT	517	MD: 0.05 (-0.31, 0.41)	-	-	1.05[25]	Serious[21]	NA[3]	No serious	No serious	Moderate
QoL – W-BQ22- change in anxiety from baseline – Glargine: once daily vs NPH: once or more than once (Lower score indicates greater wellbeing)											
Witthaus 2001	RCT	517	MD: 0.22 (-0.17, 0.61)	-	-	1.13[26]	Serious[21]	NA[3]	No serious	No serious	Moderate
QoL – W-BQ22- change in energy from baseline – Glargine: once daily vs NPH: once or more than once (Higher score indicates greater wellbeing)											
Witthaus 2001	RCT	517	MD: -0.07 (-0.40, 0.26)	-	-	0.96[32]	Serious[21]	NA[3]	No serious	No serious	Moderate
QoL – W-BQ22- change in positive wellbeing from baseline – Glargine: once daily vs NPH: once or more than once (Higher score indicates greater wellbeing)											
Witthaus 2001	RCT	517	MD: 0.04 (-0.39, 0.47)	-	-	1.25[33]	Serious[21]	NA[3]	No serious	No serious	Moderate

[1] *MID = 0.5 of the median standard deviation of the comparison group (SD= 5.1565).*
[2] *Limited information on allocation concealment and randomisation. Downgrade 1 level for serious risk of bias.*
[3] *Inconsistency not applicable for single study.*
[4] *Participants received once daily glargine U100 but twice (or more) daily NPH which does not match review protocol. Downgrade 1 level for serious indirectness.*
[5] *MID = 0.5 of the median standard deviation of the comparison group (SD= 2.053).*
[6] *MID = 0.5 of the median standard deviation of the comparison group (SD= 0.67).*
[7] *MID = 0.5 of the median standard deviation of the comparison group (SD= 6.2).*
[8] *Participants received once daily glargine U100 but 4-times daily NPH which does not match review protocol. Downgrade 1 level for serious indirectness.*
[9] *Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.*
[10] *MID = 0.5 of the median standard deviation of the comparison group (SD= 2.32).*
[11] *Fulcher 2005, Home 2005 and Ratner 2000.*
[12] *Greater than 33.3% of the weight in meta-analysis from studies with moderate and high risk of bias. Downgrade 1 level for serious risk of bias.*
[13] *I^2 was between greater than 33.3% and 66.7%. Downgrade 1 level for serious inconsistency.*

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[14] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*
[15] *No information about randomisation or allocation concealment, Higher percentage of people withdrew from NPH arm than glargine arm. Downgrade 2 levels for very serious risk of bias.*
[16] *Greater than 33.3% of the weight in meta-analysis from studies with moderate risk of bias. Downgrade 1 level for serious risk of bias.*
[17] *Fulcher 2005, Home 2005 and Bolli 2009*
[18] *Fulcher 2005, Bolli 2009 and Ratner 2000*
[19] *Open label trial could have influenced subjective outcomes in study. Additionally, study provided no information on allocation and randomisation process. Downgrade 1 level for serious risk of bias.*
[20] *MID = 0.5 of the median standard deviation of the comparison group (SD= 5.86).*
[21] *Open label trial could have influenced subjective outcomes in study. Downgrade 1 level for serious risk of bias.*
[22] *MID = 0.5 of the median standard deviation of the comparison group (SD= 1.39).*
[23] *MID = 0.5 of the median standard deviation of the comparison group (SD= 1.28).*
[24] *MID = 0.5 of the median standard deviation of the comparison group (SD= 6.67).*
[25] *MID = 0.5 of the median standard deviation of the comparison group (SD= 2.09).*
[26] *MID = 0.5 of the median standard deviation of the comparison group (SD= 2.26).*
[27] *MID = 0.5 of the median standard deviation of the comparison group (SD= 1.91).*
[38] *MID = 0.5 of the median standard deviation of the comparison group (SD= 2.49).*
**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Glargine U300 vs Glargine U100

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Patients achieving HbA1c <7% - once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
3[1]	RCT	1336	RR:0.92 (0.76, 1.12)	23 per 100 people	21 per 100 people (18 less, 26 more)	-	Serious[2]	No serious	No serious	Serious[3]	Low
Percentage of time spent in target glucose range – once daily											
2[4]	RCT	663	MD: 0.35 (-1.65, 2.35)	-	-	-	Serious[2]	No serious	No serious	No serious	Moderate
Change in weight – once daily											
2[5]	RCT	792	MD: -0.50 (-0.89, -0.11)	-	-	1.6[6]	Serious[2]	No serious	No serious	No serious	Moderate
Adverse events- once daily											
5[7]	RCT	1588	RR: 1.08 (0.98, 1.19)	44 per 100 people	47 per 100 people (43 less, 52 more)	-	Serious[2]	No serious	No serious	Serious[3]	Low
Serious AEs - once daily											
3[1]	RCT	1430	RR: 0.95 (0.61, 1.47)	5 per 100 people	5 per 100 people (3 less, 8 more)	-	Serious[2]	No serious	No serious	Serious[3]	Low
Injection site reactions – Once daily											
3[1]	RCT	1430	RR: 1.67 (0.52, 5.33)	1 per 100 people	1 per 100 people (0 less, 1 more)	-	Serious[2]	No serious	No serious	Serious[3]	Low
QoL- Change in EQ-5D utility index (Higher score indicates better QoL)											
Home 2015	RCT	546	MD: 0.03 (0.00, 0.06)	-	-	0.083[8]	Serious[9]	NA[10]	No serious	No serious	Moderate
QoL- Change in DTSQ (Higher score indicates better satisfaction)											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Home 2015	RCT	546	MD: -0.40 (-1.23, 0.43)	-	-	2.48[11]	Serious[9]	NA[10]	No serious	No serious	Moderate

[1] *Home 2015, Matsuhisa 2016 A, Pettus 2019*
[2] *Greater than 33.3% of the weight in meta-analysis from studies with moderate risk of bias. Downgrade 1 level for serious risk of bias.*
[3] 95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.
[4] *Bergenstal 2017 and Pettus 201*
[5] *Home 2015, Matsuhsia 2016 A*
[6] *Most conservative SD used to calculate MID. MID = 0.5 of the median standard deviation of the comparison group (SD= 3.2).*
[7] *Bergenstal 2017, Home 2015, Jinnouchi 2015, Matsuhsia 2016 A, Pettus 2019.*
[8] *MID = 0.5 of the median standard deviation of the comparison group (SD= 0.1652).*
[9] *Open label trial could have influenced subjective outcomes in study. Downgrade 1 level for serious risk of bias.*
[10] *Inconsistency not applicable for single study.*
[11] *MID = 0.5 of the median standard deviation of the comparison group (SD= 4.9568).*
**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in weight (kg)- once daily											
Matsuhisa 2016 B	RCT	243	MD: -0.35 (-0.91, 0.21)	-	-	1.05[1]	Serious[2]	NA[3]	No serious	No serious	Moderate
Adverse events – once daily											
Home 2018	RCT	549	RR: 1.23 (0.85, 1.77)	68 per 100 people	84 per 100 people (58 less ,120)	-	Serious[4]	NA[3]	No serious	Serious[5]	Low
Serious AEs– once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Home 2018	RCT	549	RR: 1.04 (0.62, 1.74)	9 per 100 people	10 per 100 people (6 less, 16 more)	-	Serious[4]	NA[3]	No serious	Serious[5]	Low
Injection site reaction- once daily											
2[6]	RCT	792	RR: 2.01 (0.61, 6.59)	1 per 100 people	2 per 100 people (1 less, 7 more)	-	Serious[7]	No serious	No serious	Serious[5]	Low
QoL- Change in EQ-5D utility index (Higher score indicates better QoL)- once daily											
Home 2018	RCT	546	MD: 0.00 (-0.03, 0.03)	-	-	0.083[8]	Serious[4]	NA[3]	No serious	No serious	Moderate
QoL- Change in DTSQ (Higher score indicates better satisfaction)– Once daily											
Home 2018	RCT	546	MD: -0.30 (-1.16, 0.56)	-	-	2.45[9]	Serious[4]	NA[3]	No serious	No serious	Moderate
QoL- Change in HFSII score (lower score indicating less fear of hypoglycaemia) – Once daily											
Home 2018	RCT	546	MD: 0.00 (-0.07, 0.07)	-	-	0.215[10]	Serious[4]	NA[3]	No serious	No serious	Moderate

[1] *MID = 0.5 of the median standard deviation of the comparison group (SD= 2.09).*
[2] *No information on allocation concealment and randomisation. Downgrade 1 level for serious risk of bias.*
[3] *Inconsistency not applicable for single study.*
[4] *Open label trial could have influenced subjective outcomes in study. Downgrade 1 level for serious risk of bias.*
[5] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*
[6] *Home 2018, Matsuhsia 2016 B.*
[7] *Greater than 33.3% of the weight in meta-analysis from studies with moderate risk of bias. Downgrade 1 level for serious risk of bias.*
[8] *MID = 0.5 of the median standard deviation of the comparison group (SD= 0.1652).*
[9] *MID = 0.5 of the median standard deviation of the comparison group (SD= 4.9).*
[10] *MID = 0.5 of the median standard deviation of the comparison group (SD= 0.43).*
**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Frequency of administration

Detemir once daily vs Detemir twice daily

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control*	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Participants achieving HbA1c <7%											
Le Floch 2009	RCT	512	RR: 0.92 (0.61, 1.39)	16 per 100 people	14 per 100 people (10 less, 22 more)	-	Not serious	NA[1]	Not serious	Serious[2]	Moderate
Frequency of hypoglycaemia (events/ patient/ 14 days)											
Le Floch 2009	RCT	512	MD: -3.00 (-5.52, 0.52)	-	-	12[3]	Not serious	NA[1]	Not serious	Not serious	High

[1] *Inconsistency not applicable for single study*

[2] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[3] MID = 0.5 of the median standard deviation of the comparison group (SD=24).

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Biosimilars

LY IGlar vs Glargine U100

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c (%) – once daily											
Belvins 2015	RCT	535	MD: 0.11 (-0.03, 0.25)	-	-	-	Serious[1]	NA[2]	No serious	No serious	Moderate
Participants achieving HbA1c <7% - once daily											
Belvins 2015	RCT	535	RR: 1.07 (0.95, 1.03)	32 per 100 people	34 per 100 people (27 less, 44 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Hypoglycaemia (all)– once daily											
Belvins 2015	RCT	535	RR: 0.99 (0.95, 1.03)	95 per 100 people	94 per 100 people (90 less, 98 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Major/ severe hypoglycaemia – once daily											
Belvins 2015	RCT	535	RR: 0.62 (0.21, 1.88)	3 per 100 people	2 per 100 people (1 less, 6 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Nocturnal hypoglycaemia – once daily											
Belvins 2015	RCT	535	RR: 1.02 (0.94, 1.11)	80 per 100 people	82 per 100 people (75 less, 89 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in weight (kg) – once daily											
Belvins 2015	RCT	535	MD: 0.00 (-2.75, 2.75)	-	-	7.89[4]	Serious[1]	NA[2]	No serious	No serious	Moderate

[1] *Insufficient information on randomisation and allocation concealment. Potential bias introduced due to adjustment of missing data. Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

[3] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[4] *MID = 0.5 of the median standard deviation of the comparison group (SD= 15.71).*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c (%) – once daily											
Blevins 2015	RCT	535	MD: 0.02 (-0.15, 0.19)	-	-	-	Serious[1]	NA[2]	No serious	No serious	Moderate
Participants achieving HbA1c <7% - once daily											
Blevins 2015	RCT	535	RR: 1.20 (0.91, 1.59)	25 per 100 people	30 per 100 people (23 less, 40 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Hypoglycaemia (all)– once daily											
Blevins 2015	RCT	535	RR: 0.99 (0.96, 1.02)	97 per 100 people	96 per 100 people (93 less, 99 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Major/ severe hypoglycaemia – once daily											
Blevins 2015	RCT	535	RR: 1.00 (0.44, 2.26)	4 per 100 people	4 per 100 people (2 less,9 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Nocturnal hypoglycaemia – once daily											
Blevins 2015	RCT	535	RR: 0.98 (0.91, 1.04)	88 per 100 people	86 per 100 people (80 less, 92 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Change in weight (kg) – once daily											
Blevins 2015	RCT	535	MD: 0.00 (-2.74, 2.75)	-	-	7.89[4]	Serious[1]	NA[2]	No serious	No serious	Moderate
Adverse events– once daily											
Blevins 2015	RCT	535	RR: 1.21 (0.61, 2.40)	5 per 100 people	6 per 100 people (3 less, 13 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Serious AEs- once daily											
Blevins 2015	RCT	535	RR: 0.83 (0.47, 1.47)	9 per 100 people	7 per 100 people (4 less, 13 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Injection site reactions- once daily											
Blevins 2015	RCT	535	RR: 2.32 (0.61, 8.89)	1 per 100 people	3 per 100 people (1 less, 10 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
QoL – Change in ITSQ total score (greater score indicates greater improvement) – once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
De Lozier 2018	RCT	535	MD: -0.16 (-2.89, 2.57)	-	-	8.05[5]	Serious[6]	NA[2]	No serious	No serious	Moderate
QoL – Change in ALBSS total score (lower score indicates greater improvement)- once daily											
De Lozier 2018	RCT	535	MD: -0.69 (-3.98, 2.60)	-	-	9.68[7]	Serious[6]	NA[2]	No serious	No serious	Moderate

[1] *Insufficient information on randomisation and allocation concealment. Potential bias introduced due to adjustment of missing data. Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

[3] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[4] *MID = 0.5 of the median standard deviation of the comparison group (SD= 15.71).*

[5] *MID = 0.5 of the median standard deviation of the comparison group (SD= 16.1).*

[6] *Open label trial. Potential bias introduced for subjective outcomes. Downgrade 1 level for serious risk of bias.*

[7] *MID = 0.5 of the median standard deviation of the comparison group (SD= 19.35).*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

MYLD-1501D vs Glargine U100

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c (%) – Once daily											
Blevins 2018	RCT	558	MD: 0.03 (-0.12, 0.18)	-	-	-	Serious[1]	NA[2]	No serious	No serious	Moderate

[1] *Insufficient information on randomisation process. Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

****Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c (%) – Once daily											
Blevins 2018	RCT	558	MD: -0.04 (-0.19, 0.11)	-	-	-	Serious[1]	NA[2]	No serious	No serious	Moderate
Change in weight (kg) – once daily											
Blevins 2018	RCT	558	MD: 0.16 (-0.41, 0.73)	-	-	1.59[3]	Serious[1]	NA[2]	No serious	No serious	Moderate
Hypoglycaemia (all)– once daily											
Blevins 2018	RCT	558	RR: 0.90 (0.78, 1.04)	61 per 100 people	55 per 100 people (48 less, 64 more)	-	Serious[1]	NA[2]	No serious	Serious[4]	Low
Major/ severe hypoglycaemia – once daily											
Blevins 2018	RCT	558	RR: 0.84 (0.38, 1.84)	5 per 100 people	4 per 100 people (2 less,9 more)	-	Serious[1]	NA[2]	No serious	Serious[4]	Low
Nocturnal hypoglycaemia – once daily											
Blevins 2018	RCT	558	RR: 1.13 (0.42, 3.09)	3 per 100 people	3 per 100 people (1 less,8 more)	-	Serious[1]	NA[2]	No serious	Serious[4]	Low
Adverse events– once daily											
Blevins 2018	RCT	558	RR: 0.93 (0.87, 1.01)	86 per 100 people	80 per 100 people (75 less, 87 more)	-	Very serious[5]	NA[2]	No serious	Serious[4]	Very low

[1] *Insufficient information on randomisation process. Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

[3] *MID = 0.5 of the median standard deviation of the comparison group (SD= 3.18).*

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[4] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[5] *Insufficient information on randomisation process. Open label design could have introduced bias for subjective outcomes. Downgrade 2 levels for very serious risk of bias.*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

MK-1239 vs Glargine U100

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c (%) – once daily											
Home 2018 B	RCT	499	MD: 0.04 (-0.19, 0.27)	-	-	-	Serious[1]	NA[2]	Serious[3]	No serious	Low
Participants achieving HbA1c <7% - once daily											
Home 2018 B	RCT	499	RR:0.97 (0.76, 1.24)	34 per 100 people	33 per 100 people (26 less, 43 more)	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Hypoglycaemia (all)– once daily											
Home 2018 B	RCT	499	RR: 0.99 (0.98, 1.01)	100 per 100 people	99 per 100 people (98 less, 101 more)	-	Serious[1]	NA[2]	Serious[3]	Serious[6]	Very low
Major/ severe hypoglycaemia – once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Home 2018 B	RCT	499	RR: 1.41 (0.89, 2.24)	11 per 100 people	15 per 100 people (10 less, 24 more)	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Nocturnal hypoglycaemia – once daily											
Home 2018 B	RCT	499	RR: 0.97 (0.93, 1.01)	97 per 100 people	94 per 100 people (90 less, 97 more)	-	Serious[1]	NA[2]	Serious[3]	No serious[4]	Low
Change in weight (kg) – once daily											
Home 2018 B	RCT	499	MD: 0.00 (-0.60, 0.60)	-	-	1.7[5]	Serious[1]	NA[2]	Serious[3]	No serious	Low

[1] *Limited information on randomisation and allocation concealment. Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

[3] *Participants received different prandial insulins. Participants were to continue with their pre-study prandial insulin regimen. Downgrade 1 level for serious indirectness.*

[4] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[5] *MID = 0.5 of the median standard deviation of the comparison group (SD= 3.4).*

[6] *Outcome met the criteria for downgrading but was not downgraded as the confidence interval was sufficiently narrow that the upper and lower bounds corresponded to clinically equivalent scenarios.*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Outcomes > 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c (%) – once daily											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Home 2018 B	RCT	499	MD: -0.02 (-0.27, 0.23)	-	-	-	Serious[1]	NA[2]	Serious[3]	No serious	Low
Participants achieving HbA1c <7% - once daily											
Home 2018 B	RCT	499	RR:0.96 (0.71, 1.29)	26 per 100 people	25 per 100 people (19 less, 27 more)	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Hypoglycaemia (all)– once daily											
Home 2018 B	RCT	499	RR: 0.99 (0.98, 1.01)	100 per 100 people	99 per 100 people (98 less, 101 more)	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Major/ severe hypoglycaemia – once daily											
Home 2018 B	RCT	499	RR: 0.95 (0.65, 1.40)	17 per 100 people	17 per 100 people (11 less,14 more)	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Nocturnal hypoglycaemia – once daily											
Home 2018 B	RCT	499	RR: 0.98 (0.95, 1.02)	97 per 100 people	95 per 100 people (92 less, 99 more)	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Change in weight (kg) – once daily											
Home 2018 B	RCT	499	MD: -0.30 (-1.02, 0.42)	-	-	2.05[5]	Serious[1]	NA[2]	Serious[3]	No serious	Low
Adverse events – once daily											
Home 2018 B	RCT	499	RR: 0.91(0.76, 1.08)	53 per 100 people	48 per 100 people (40	-	Very serious[6]	NA[2]	Serious[3]	Serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					less, 54 more)						
Serious AEs – once daily											
Home 2018 B	RCT	499	RR: 0.82 (0.49, 1.37)	12 per 100 people	10 per 100 people (6 less,16 more)	-	Very serious[6]	NA[2]	Serious[3]	Serious[4]	Very low
Injection site reactions											
Home 2018 B	RCT	499	RR: 2.14 (0.20, 23.46)	0 per 100 people	1 per 100 people (0 less, 9 more)	-	Very serious[6]	NA[2]	Serious[3]	Serious[4]	Very low

[1] *Limited information on randomisation and allocation concealment. Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

[3] *Participants received different prandial insulins. Participants were to continue with their pre-study prandial insulin regimen. Downgrade 1 level for serious indirectness.*

[4] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[5] *MID = 0.5 of the median standard deviation of the comparison group (SD= 4.1).*

[6] *Limited information on randomisation and allocation concealment. Open label design could have introduced bias for subjective outcomes. Downgrade 2 levels for very serious risk of bias.*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

GP40061 vs Glargine U100

Outcomes ≤ 6 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c (%)– Once daily											
Karanova 2020	RCT	180	MD: 0.11 (-0.19, 0.41)	-	-	-	Serious[1]	NA[2]	Serious[3]	No serious	Moderate
Participants achieving glycaemic control– once daily											
Karanova 2020	RCT	180	RR: 0.79 (0.43, 1.45)	21 per 100 people	17 per 100 people (9 less,31 more)	-	Serious[1]	NA[2]	Serious[3]	Serious[4]	Low
Change in weight (kg)- once daily											
Karanova 2020	RCT	180	MD: -0.20 (-0.80, 0.40)	-	-	0.995[5]	Serious[1]	NA[2]	Serious[3]	No serious	Low
Major/ severe hypoglycaemia – once daily											
Karanova 2020	RCT	180	RR: 0.44 (0.14, 1.39)	10 per 100 people	4 per 100 people (1 less,14 more)	-	Very serious[6]	NA[2]	Serious[3]	Serious[4]	Very low
Nocturnal hypoglycaemia – once daily											
Karanova 2020	RCT	180	RR: 0.82 (0.56, 1.19)	42 per 100 people	35 per 100 people (24 less, 50 more)	-	Very serious[6]	NA[2]	Serious[3]	Serious[4]	Very low
Adverse events – once daily											
Karanova 2020	RCT	180	RR: 1.50 (0.56, 4.04)	7 per 100 people	10 per 100 people (4, 27)	-	Very serious[6]	NA[2]	Serious[3]	Serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Serious AEs– once daily											
Karanova 2020	RCT	180	RR: 1.00 (0.14, 6.95)	2 per 100 people	2 per 100 people (0 less, 15 more)	-	Very serious[6]	NA[2]	Serious[3]	Serious[4]	Very low
Injection site reactions											
Karanova 2020	RCT	180	RR: 3.00 (0.32, 28.30)	1 per 100 people	3 per 100 people (0 less,8 more)	-	Very serious[6]	NA[2]	Serious[3]	Serious[4]	Very low
QoL – Change in DTSQ total score (higher score indicating greater satisfaction) – once daily											
Karanova 2020	RCT	180	MD: 0.29 (-1.79, 2.37)	-	-	3.59[7]	Very serious[6]	NA[2]	Serious[3]	No serious	Very low

[1] *Limited information on randomisation, allocation concealment and method of analysis. Downgrade 1 level for serious risk of bias.*

[2] *Inconsistency not applicable for single study.*

[3] *Study does not highlight which bolus insulins were used. Downgrade 1 level for serious indirectness.*

[4] *95% confidence interval crosses the line of no effect. Downgrade 1 level for serious imprecision.*

[5] *MID = 0.5 of the median standard deviation of the comparison group (SD= 1.99*).

[6] *Limited information on randomisation, allocation concealment and method of analysis. Open label design could have had an influence on subjective outcomes. Downgrade 2 levels for very serious risk of bias*.

[7] *MID = 0.5 of the median standard deviation of the comparison group (SD=7.18).*

**** Derived by taking the overall number of event/ total number of participants and multiplying by 100.***

Appendix J – GRADE table for NMA

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Change in HbA1c (%)								
28 studies	RCT	9119	See appendix K	Serious[1]	No serious[2]	No serious[3]	Serious[4]	Low
All hypoglycaemia								
27 studies	RCT	10,251	See appendix K	Serious[1]	No serious[2]	No serious[3]	Very serious[5]	Very low
Severe/ major hypoglycaemia								
27 studies	RCT	10,584	See appendix K	Serious[1]	No serious[2]	No serious[3]	Very serious[6]	Very low
Nocturnal hypoglycaemia								
22 studies	RCT	8092	See appendix K	Serious[1]	No serious[2]	No serious[3]	Serious[7]	Low

[1] *Greater than 33.3% of studies in the NMA were at moderate or high risk of bias. Downgrade 1 level for serious risk of bias.*

[2] *Fewer than 33.3% studies in the NMA were partially indirect. The overall network was not downgraded.*

[3] *The DIC of the inconsistency model was not 3 points lower than the DIC of the consistency model. See Appendix K for DIC.*

[4] *The evidence did not identify any meaningful differences between the long-acting insulins, but the evidence did aid the committee to draw the conclusion that there was complete equivalence. Downgrade 1 level for serious imprecision.*

[5] *The evidence did not identify any meaningful differences and did not demonstrate equivalence. Downgrade 2 levels for very serious imprecision.*

[6] *Some significant evidence was identified which supported the use of detemir twice daily compared to NPH once/twice daily and detemir once/twice daily when compared to NPH once/twice daily. However, 95% confidence intervals were wide demonstrating uncertainty in the evidence. Downgrade 2 levels for very serious imprecision.*

[7] *Committee were able to draw some conclusions from the evidence particularly for insulins such as detemir twice daily and degludec U100 once daily. However, there was uncertainty in the evidence for all other long-acting insulins. Downgrade 1 level for serious risk of bias.*

Appendix K – Network meta-analysis

General Methods

For details of the generic methods adopted for these analyses, please see Appendix B.

Analyses undertaken

During protocol development, the committee identified HbA1c and hypoglycaemia, particularly severe/major and nocturnal hypoglycaemia as critical outcomes. The committee highlighted that while mild hypoglycaemic events can be treated by the individual, severe/major hypoglycaemic events require assistance from another person and if these are not treated immediately, these can be dangerous. Nocturnal hypoglycaemic events also occur more frequently that severe hypoglycaemic events. These events can greatly impact the patient's quality of life and mental health outcomes.

Based on these discussions, the decision was made to conduct separate NMAs for outcomes change in HbA1c, severe hypoglycaemia and nocturnal hypoglycaemia.

In the review, studies exploring the following comparisons were identified:

- **Detemir vs NPH:**
  - Detemir once daily vs NPH once daily
  - Detemir once/ twice daily vs NPH once/ twice daily
  - Detemir twice daily vs NPH twice daily
- **Detemir vs Glargine U100:**
  - Detemir twice daily vs glargine once daily
  - Detemir once/twice daily vs glargine once daily
- **Degludec U100 vs Glargine U100:**
  - Degludec U100 once daily vs glargine U100 once daily
- **Degludec U200 vs Glargine U300:**
  - Degludec U200 once daily vs glargine U300 once daily
- **Glargine U100 vs NPH:**
  - Glargine U100 once daily vs NPH 4x daily
  - Glargine U100 once daily vs NPH once/ twice daily
  - Glargine U100 once daily vs NPH twice daily
  - Glargine U100 once daily NPH twice or more
- **Degludec U100 vs Detemir:**
  - Degludec U100 once daily vs detemir once daily
- **Glargine U300 vs Glargine U100:**
  - Glargine U300 once daily vs glargine U100 once daily
- **Glargine U100 once daily vs Glargine U100 twice daily**
- **Detemir once daily vs Detemir twice daily**
- **Glargine biosimilar (GP40061) vs glargine U100:**
  - Biosim. once daily vs glargine U100 once daily
- **Glargine biosimilar (MK-1293) vs glargine U100:**
  - Biosim. once daily vs glargine U100 once daily
- **Glargine biosimilar (MYL-1501D) vs glargine U100:**
  - Biosim. once daily vs glargine U100 once daily
- **Glargine biosimilar (LY2963016) vs glargine U100:**
  - Biosim. once daily vs glargine U100 once daily
- **Degludec vs Glargine (concentration not defined)**
  - Degludec once daily vs glargine twice daily

- Degludec once daily vs glargine once daily

A number of studies were also excluded from the analyses. This included five studies which examined the effectiveness of biosimilars compared the intervention to the originator glargine [Blevins 2015, Blevins 2018, Perez-Nieves 2018, Home 2018 and Karanova 2020]. As the aim of the review was not to compare biosimilars to the originator insulin, these studies were not included in the analyses.

Two studies were identified [Iga 2017 and Onda 2017] which compared degludec with glargine. These studies did not specify the concentration of the insulins and were therefore not included in the analyses.

Two studies were identified which compared glargine U100 with NPH four time daily [Porcellati 2000 and Rossetti 2003]. These studies were partially indirectly applicable to this review. The committee further highlighted that NPH four times daily is not used in practice and therefore these studies were not included in the NMAs.

One further study was identified that compared glargine U100 once daily with NPH twice or more daily [Bolli 2009]. The study reported that within the NPH group, 62 participants received NPH twice daily, 10 received NPH three times daily and 4 received NPH. As majority of participants received NPH twice daily, the study was included in the analyses as a separate node and was downgraded accordingly.

A number of studies were identified which included patients receiving both once and daily regimens [Zachariah 2011, Home 2005, Ratner 2000, Raskin 2000, Rosenstock 2000, Heller 2009 and Renard 2011]. Where possible, data for the two subgroups were extracted, however where this data was not available, data was extracted and used in the analyses as mixed regimens.

Detemir twice daily was chosen as the baseline comparator as this was recommended in the 2015 recommendation. It should also be noted that in the 2015 NMA, NPH twice daily was chosen as the baseline comparator as this was the ‘standard’ human long-acting insulin. However, the committee stated that clinical practice has changed since 2015 and NPH is not commonly used.

Additionally, the review protocol also states that outcome data would be grouped as either short term outcomes (≤6 months) or long-term outcomes (>6 months). Further committee discussions highlighted that long-acting insulins are quick acting and there should not be differences in long-term and short-term effects. Furthermore, in clinical practice, the use of long-acting insulins goes beyond 6 months. Based on these discussions, it was agreed that all follow up data would be combined in the NMAs. Also, where trials reported data at multiple time-point, the data from the longest time point was used in the analysis.

Model selection

Potential models

Change in HbA1c

Different types of models were discussed with the committee which included a split approach in which all long-acting insulins and frequency of administration were analysed separately or a lumped approach in which identical interventions could be grouped together. The committee opted for the split approach in which agents were separated out by frequency (See appendix G for NMA pairwise analysis).

Overall, 28 trials (reported across 32 studies) were identified which reported change in HbA1c or provided information for change in HbA1c to be calculated (methods highlighted in Appendix B). Studies included in the analysis are highlighted in Table 1.

The change in HbA1c pairwise analyses are shown in appendix G. Overall, there was low heterogeneity, but subgroup differences were identified in studies comparing NPH once/twice daily with glargine U100 once daily (I^2= 66.4%). The pairwise analysis also demonstrated that there was serious heterogeneity in the studies reporting the outcome ≤6 months (I^2= 68%). In this analysis, heterogeneity was driven by one three arm study (Pieber 2000) which compared different formulations of glargine with NPH.

Additionally, subgroup differences were identified in studies comparing glargine U100 once daily with degludec U100 once daily. In this analysis, heterogeneity was driven by one three arm trial study (Mathieu 2013) which compared degludec U100 once daily, glargine U100 and degludec forced-flex. In the forced-flex arm the insulin was administered at fixed intervals with a minimum of 8 and a maximum of 40 hours between injections. Data on degludec forced-flex was not included in the analysis.

Table 1: Studies included in change in HbA1c analysis

Study	Intervention 1	Intervention 2
De Leeuw 2005	Detemir twice daily	NPH twice daily
Home 2004	Detemir twice daily	NPH twice daily
Kolendorf 2006	Detemir twice daily	NPH twice daily
Pieber 2005	Detemir twice daily	NPH twice daily
Standl 2004	Detemir twice daily	NPH twice daily
Vague 2003	Detemir twice daily	NPH twice daily
Le Flouch 2009 (ADAPT)	Detemir twice daily	Detemir once daily
Russell- Jones 2004	Detemir once daily	NPH once daily
van Golen 2013	Detemir once daily	NPH once daily
Zachariah 2011	Detemir once/twice daily	NPH once/twice daily
Heller 2009	Detemir once/twice daily	Glargine U100 once daily
Renard 2009	Detemir once/twice daily	Glargine U100 once daily
Birkeland 2011+ Home 2012	Glargine U100 once daily	Degludec U100 once daily
Heller 2012 + Bode 2013 (BEGIN Trial)	Glargine U100 once daily	Degludec U100 once daily
Mathieu 2013 (BEGIN Flex T1)	Glargine U100 once daily	Degludec U100 once daily
Davies 2014	Detemir once daily	Degludec U100 once daily
Home 2005	NPH once/twice daily	Glargine U100 once daily
Pieber 2000	NPH once/twice daily	Glargine U100 once daily
Raskin 2000	NPH once/twice daily	Glargine U100 once daily
Ratner 2000	NPH once/twice daily	Glargine U100 once daily
Rosenstock 2000	NPH once/twice daily	Glargine U100 once daily
Chatterjee 2007	NPH twice daily	Glargine U100 once daily
Bolli 2009	Glargine U100 once daily	NPH twice or more daily
Bergenstal 2017	Glargine U100 once daily	Glargine U300 once daily
Home 2015 + Home 2018 (EDITION 4)	Glargine U100 once daily	Glargine U300 once daily
Matsuhisa 2016 A + Matsuhisa 2016 B (EDITION JP1)	Glargine U100 once daily	Glargine U300 once daily

Study	Intervention 1	Intervention 2
Pettus 2019	Glargine U100 once daily	Glargine U300 once daily
Ashwell 2006	Glargine U100 once daily	Glargine U100 twice daily

Hypoglycaemia

As with the change in HbA1c model, a split approach was used to model the data, and all follow up data was combined in the analysis.

Economic modelling required data on severe hypoglycaemia, non-severe hypoglycaemia, proportion of nocturnal hypoglycaemic episodes that are severe and proportion of nocturnal hypoglycaemic episodes that were non-severe. Based on these requirements the following approach was considered:

- Conducting an NMA for all hypoglycaemic events
- modelling the probability that an event is severe/major given that a patient had an event
- modelling the probability that an event is nocturnal given a patient had an event.

However, with this approach only studies which reported all hypoglycaemic events and severe and nocturnal hypoglycaemic events could be included in the analysis. This meant for the severe hypoglycaemia model, 2 studies would be excluded [De Leeuw 2005 and Renard 2011]. Additionally, studies which only reported event data (number of events for a given total exposure) could be included. This would mean that two further studies [Home 2005 and Pieber 2000] would be excluded from the analysis as these reported risk data (number of patients who experienced at least one event out of total randomised).

To maximise the number of studies included in the analysis the following approach was used which would also provide the data required for economic modelling:

- Conducting an NMA for all hypoglycaemic events
- Conducting an NMA for severe/major hypoglycaemic events
- modelling the probability that an event is nocturnal given a patient had an event.

Additionally, as studies reported both risk and rate data, a shared parameters approach was utilised as described in Keeney (2018) as this would allow both sets of data to be incorporated into the model (see appendix B for methods).

It should also be noted that, 3 studies [Heise 2012, Jinnouchi 2015 and Heise 2017] followed up the participants for less than 4 weeks. As the follow up time was short, these studies were not included in the analysis. Due to this, direct evidence comparing degludec U200 once daily and glargine U300 once daily was not included in the analysis.

All hypoglycaemia

27 trials (reported across 31 studies) were included. Trials were identified which reported data at multiple time points. In the case of such trials, the data from the longest time point was used in the analysis. This approach was also applied to the severe hypoglycaemia and nocturnal hypoglycaemia models.

All hypoglycaemia pairwise analyses are shown in appendix G. Due to the nature of the evidence, very high heterogeneity was identified. As rate data permits multiple events per person to be captured, uncertainty levels are tighter which makes it more likely for between study differences to be picked up.

Some subgroup differences were identified. For example, subgroup differences were identified in the studies comparing detemir twice daily with NPH twice daily (I^2= 73.2%). Most studies favoured detemir, however one three arm trial (Pieber 2005) favoured NPH. This study compared detemir (morning and dinner), detemir (morning and bedtime) and NPH (morning and bedtime). For direct comparison, only data from detemir (morning and bedtime) was included.

Some heterogeneity can also be attributed to definitions used in studies. For example, subgroup differences were also identified in studies comparing glargine U100 once daily with NPH once/ twice daily (I^2= 98.2%). Such a difference was not seen in the risk data, but it was identified that the two studies used in the analysis used varying definitions of hypoglycaemia. Ratner 2000 defined hypoglycaemia as blood glucose level of < 2.0 mmol/l and further divided the episodes as severe hypoglycaemia (a symptomatic event requiring assistance from another individual) and nocturnal hypoglycaemia. Raskin 2000 defined hypoglycaemia as symptomatic hypoglycaemia, severe hypoglycaemia (an event with symptoms consistent with hypoglycaemia in which the subject required assistance from another person and which was accompanied by a blood glucose level of <2.0 mmol/l or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration) and nocturnal hypoglycaemia.

Studies included in the analysis are highlighted in Table 2. Overall, 4 studies provided risk data and 23 studies provided rate data.

Table 2: Studies included in all hypoglycaemia analysis

Study	Risk data	Rate data
Detemir twice daily vs NPH twice daily		
Home 2004		✓
Kolendorf 2006		✓
Pieber 2005		✓
Standl 2004		✓
Vague 2003		✓
Detemir twice daily vs Glargine U100 once daily		
Pieber 2007		✓
Detemir once daily vs NPH once daily		
Russell- Jones 2004		✓
Hermansen 2001		✓
Detemir once/twice daily vs NPH once/twice daily		
Bartley 2008		✓
Glargine U100 once daily vs Detemir once/twice daily		
Heller 2009		✓
Glargine U100 once daily vs Degludec U100 once daily		
Birkeland 2011+ Home 2012		✓
Heller 2012 + Bode 2013 (BEGIN Trial)		✓
Mathieu 2013 (BEGIN Flex T1)		✓
Lane 2017 (SWITCH 1)		✓
Detemir once daily vs Degludec U100 once daily		
Davies 2014		✓
Iwamoto 2013		✓
Glargine U100 once daily vs NPH once/twice daily		
Home 2005	✓	

Study	Risk data	Rate data
Raskin 2000		✓
Ratner 2000		✓
Rosenstock 2000	✓	
NPH twice daily vs Glargine U100 once daily		
Chatterjee 2007		✓
Pieber 2000	✓	
Glargine U100 once daily vs NPH once daily		
Fulcher 2005		✓
Pieber 2000	✓	
Glargine U100 once daily vs Glargine U300 once daily		
Home 2015 + Home 2018 (EDITION 4)		✓
Matsuhisa 2016 A + Matsuhisa 2016 B (EDITION JP1)		✓
Pettus 2019	✓	
Glargine U100 once daily vs Glargine U100 twice daily		
Ashwell 2006		✓
NPH once daily vs NPH twice daily		
Pieber 2000	✓	

See appendix G for forest plots of the pairwise risk and rate data.

Severe/major hypoglycaemia

32 trials (reported across 36 studies) reported data on severe hypoglycaemia. Out of these 32 studies, 5 studies [Ashwell 2006, Zachariah 2011, Iwamoto 2013, Porcellati 2004 and Rossetti 2003] were excluded as these reported zero events in either one or both arms of the trial.

Severe/major hypoglycaemia pairwise analyses are shown in appendix G. Due to the nature of the evidence, heterogeneity was identified but overall, the rate estimates from different studies were in line with each other.

Overall, 27 studies were included in the analysis. Six studies reported risk data and 21 studies reported rate data. Studies included in the analysis are highlighted in Table 3.

Table 3: Studies included in severe/major hypoglycaemia analysis

Study	Risk data	Rate data
Detemir twice daily vs NPH twice daily		
Home 2004		✓
Kolendorf 2006		✓
Pieber 2005		✓
Standl 2004		✓
Vague 2003		✓
De Leeuw 2005	✓	
Detemir twice daily vs Glargine U100 once daily		
Pieber 2007		✓
Detemir once daily vs NPH once daily		
Russell- Jones 2004		✓

Study	Risk data	Rate data
Hermansen 2001		✓
Detemir once/twice daily vs NPH once/twice daily		
Bartley 2008		✓
Glargine U100 once daily vs Detemir once/twice daily		
Heller 2009		✓
Renard 2009	✓	
Glargine U100 once daily vs Degludec U100 once daily		
Birkeland 2011+ Home 2012		✓
Heller 2012 + Bode 2013 (BEGIN Trial)		✓
Mathieu 2013 (BEGIN Flex T1)		✓
Lane 2017 (SWITCH 1)		✓
Detemir once daily vs Degludec U100 once daily		
Davies 2014		✓
Glargine U100 once daily vs NPH once/twice daily		
Home 2005	✓	
Raskin 2000		✓
Ratner 2000		✓
NPH twice daily vs Glargine U100 once daily		
Chatterjee 2007		✓
Pieber 2000	✓	
Glargine U100 once daily vs NPH once daily		
Fulcher 2005		✓
Pieber 2000	✓	
Glargine U100 once daily vs Glargine U300 once daily		
Bergenstal 2017	✓	
Home 2015 + Home 2018 (EDITION 4)		✓
Matsuhisa 2016 A + Matsuhisa 2016 B (EDITION JP1)		✓
Pettus 2019	✓	

See appendix G for forest plots of the pairwise risk and rate data.

Nocturnal hypoglycaemia

With the conditional probabilities approach, only studies that reported both all hypoglycaemic events and nocturnal hypoglycaemic events could be included. Additionally, studies which reported risk data would be excluded from the analysis.

Severe/major hypoglycaemia pairwise analyses are shown in appendix G. Due to the nature of the evidence, heterogeneity was identified but overall, the rate estimates from different studies were in line with each other.

Overall, 22 trials (reported across 26 studies) were included in the analysis. Studies included in the analysis are highlighted in Table 4.

Table 4: Studies included in nocturnal hypoglycaemia analysis

Study	Intervention 1	Intervention 2
Home 2004	Detemir twice daily	NPH twice daily

Study	Intervention 1	Intervention 2
Kolendorf 2006	Detemir twice daily	NPH twice daily
Pieber 2005	Detemir twice daily	NPH twice daily
Standl 2004	Detemir twice daily	NPH twice daily
Vague 2003	Detemir twice daily	NPH twice daily
Pieber 2007	Detemir twice daily	Glargine U100 once daily
Russell- Jones 2004	Detemir once daily	NPH once daily
Bartley 2008	Detemir once/twice daily	NPH once/twice daily
Heller 2009	Detemir once/twice daily	Glargine U100 once daily
Birkeland 2011+ Home 2012	Glargine U100 once daily	Degludec U100 once daily
Heller 2012 + Bode 2013 (BEGIN Trial)	Glargine U100 once daily	Degludec U100 once daily
Mathieu 2013 (BEGIN Flex T1)	Glargine U100 once daily	Degludec U100 once daily
Lane 2017	Glargine U100 once daily	Degludec U100 once daily
Davies 2014	Detemir once daily	Degludec U100 once daily
Iwamoto 2013	Detemir once daily	Degludec U100 once daily
Raskin 2000	NPH once/twice daily	Glargine U100 once daily
Ratner 2000	NPH once/twice daily	Glargine U100 once daily
Chatterjee 2007	NPH twice daily	Glargine U100 once daily
Fulcher 2005	NPH once daily	Glargine U100 once daily
Home 2015 + Home 2018 (EDITION 4)	Glargine U100 once daily	Glargine U300 once daily
Matsuhisa 2016 A + Matsuhisa 2016 B (EDITION JP1)	Glargine U100 once daily	Glargine U300 once daily
Ashwell 2006	Glargine U100 once daily	Glargine U100 twice daily

See appendix G for forest plots of the pairwise data.

Choosing the best model

Both fixed effects and random effects models were explored, with final model selection for each network based on the methods described in Appendix B.

Goodness-of-fit measures for the candidate models are presented in Table 5. The following observations can be made:

- For change in HbA1c, the DIC for the random effects model was lower than the fixed effects model. This was not 3 points lower as highlighted in Appendix B, however, the total residual deviance demonstrated a better fit by more than 3 points with the random effects model, and so the random effects model was selected.
- For the hypoglycaemic outcomes, the DIC for the random effects model was lower than the fixed effects model and the total residual deviance demonstrated a better fit with random effects model, and so the random effects models were selected.

Inconsistency checks were performed using the random effects model, and the model fit statistics of both the consistency and inconsistency models are presented in Table 6, which provide a global assessment of inconsistency. Additionally, contributions of each data-point to the posterior mean deviance for the random effect consistency and inconsistency models were plotted to identify studies contributing to inconsistency. Points on either model with a deviance of greater than 2 indicate data with some lack of fit, and of those, points which are substantially below the line of equality indicate studies which are potentially inconsistent.

For change in HbA1c, there is no global evidence of inconsistency with similar posterior mean deviance and higher DIC for the random effect inconsistency model compared to the consistency model (Table 6). Figure 1 also shows that points [18,1] and [18,2] demonstrated a deviance greater than 2, indicating a lack of fit, but there is no evidence of inconsistency (points below the line of equality). These points corresponded to the study Pieber 2000. This study was a 3-arm trial which compared 2 different formulations of glargine U100 (HOE 901 [30] which included 30µg/ml of zinc and HOE 901[80] which included 80µg/ml of zinc) with NPH once or twice daily and followed participants for 4 weeks. In this review, only data from the HOE 901 [30] and NPH once/twice daily arm was included as the committee highlighted that HOE 901 [80] was not relevant to current clinical practice.

For all hypoglycaemia, severe/major hypoglycaemia and nocturnal hypoglycaemia, there was no meaningful difference in residual deviance or DIC between the random effect consistency model and inconsistency model, suggesting no global evidence of inconsistency (Table 6). Figure 2,3 and 4 show there are no points indicating lack of fit and further highlight that there were no major inconsistencies in these models.

Table 5: Model fit statistics used to select fixed or random effect models for all outcomes

Outcomes	Number of studies	Datapoints	FE/RE	Total residual deviance	DIC	Standard deviation of random effects distribution	Preferred model
Change in HbA1c	28 trials	56	**FE**	60.87	-88.229	n/a	RE
			RE	54.14	-89.055	0.06362	
All hypoglycaemia	27 trials	55	**FE**	719.7	1234.100	n/a	RE
			RE	55.07	586.618	0.2392	
Severe/ major hypoglycaemia	32 trials	54	**FE**	99.87	400.291	n/a	RE
			RE	55.44	368.046	0.4516	
Nocturnal hypoglycaemia	22 trials	44	**FE**	212.4	573.627	n/a	RE
			RE	45.2	418.042	0.3151	

Table 6: Consistency and inconsistency model fit statistics for all outcomes

Outcomes	Model	Total residual deviance	DIC	Standard deviation of random effects distribution
Change in HbA1c	**Consistency RE**	54.14	-89.055	0.06362
	Inconsistency RE	54.85	-86.422	0.06548
All hypoglycaemia	**Consistency RE**	55.07	586.618	0.2392
	Inconsistency RE	55.36	587.704	0.2494
Severe/ major hypoglycaemia	**Consistency RE**	55.44	368.046	0.4516
	Inconsistency RE	56.44	370.471	0.4266
Nocturnal hypoglycaemia	**Consistency RE**	45.2	418.042	0.3151
	Inconsistency RE	45.37	418.749	0.2984

Figure 1: Deviance contributions for the random effect consistency and inconsistency model for change in HbA1c

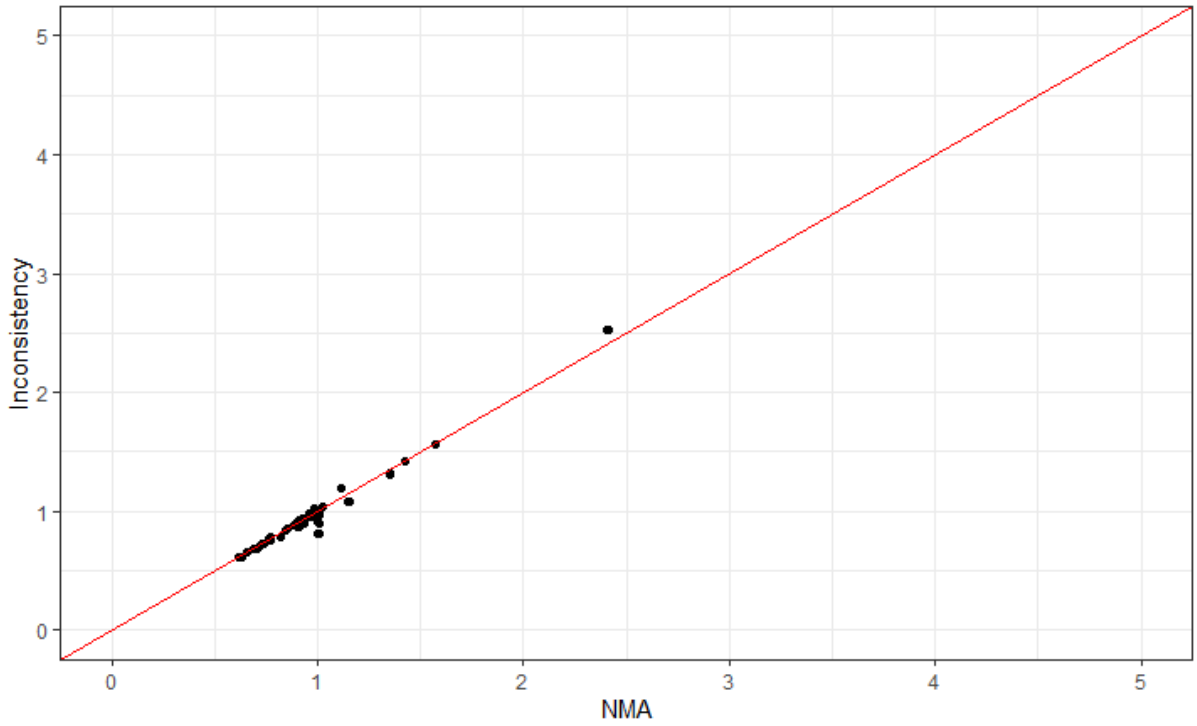


Figure 2: Deviance contributions for the random effect consistency and inconsistency model for all hypoglycaemia

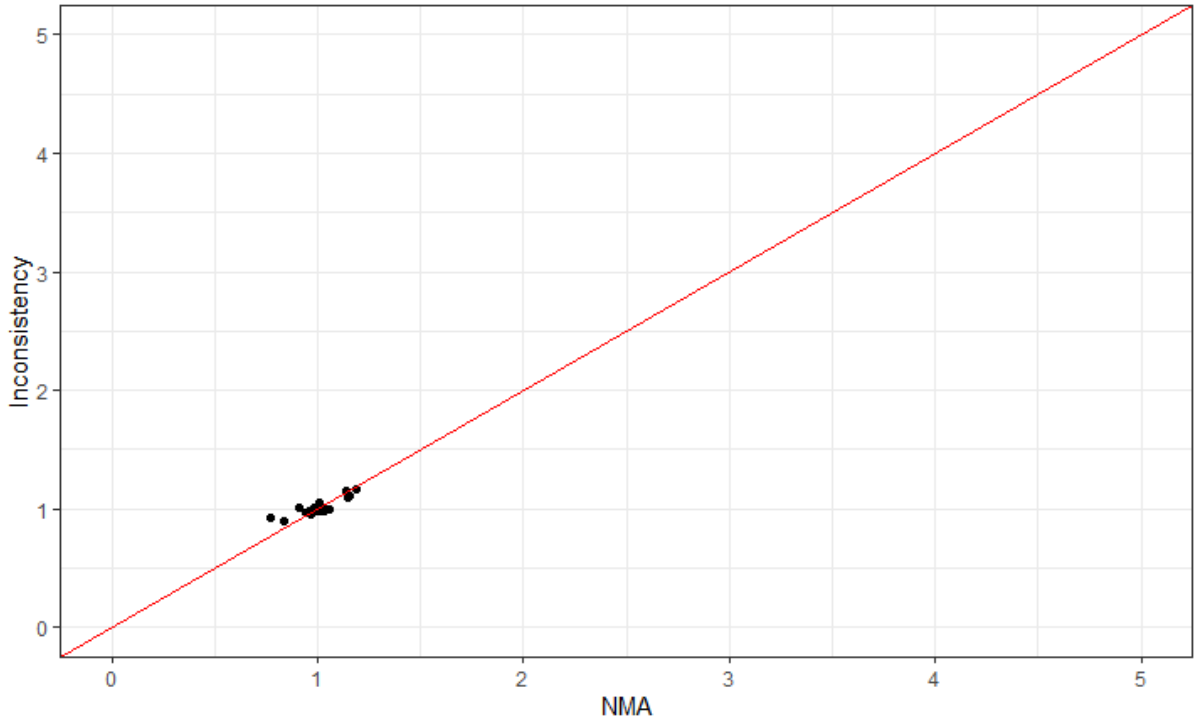


Figure 3: Deviance contributions for the random effect consistency and inconsistency model for severe hypoglycaemia

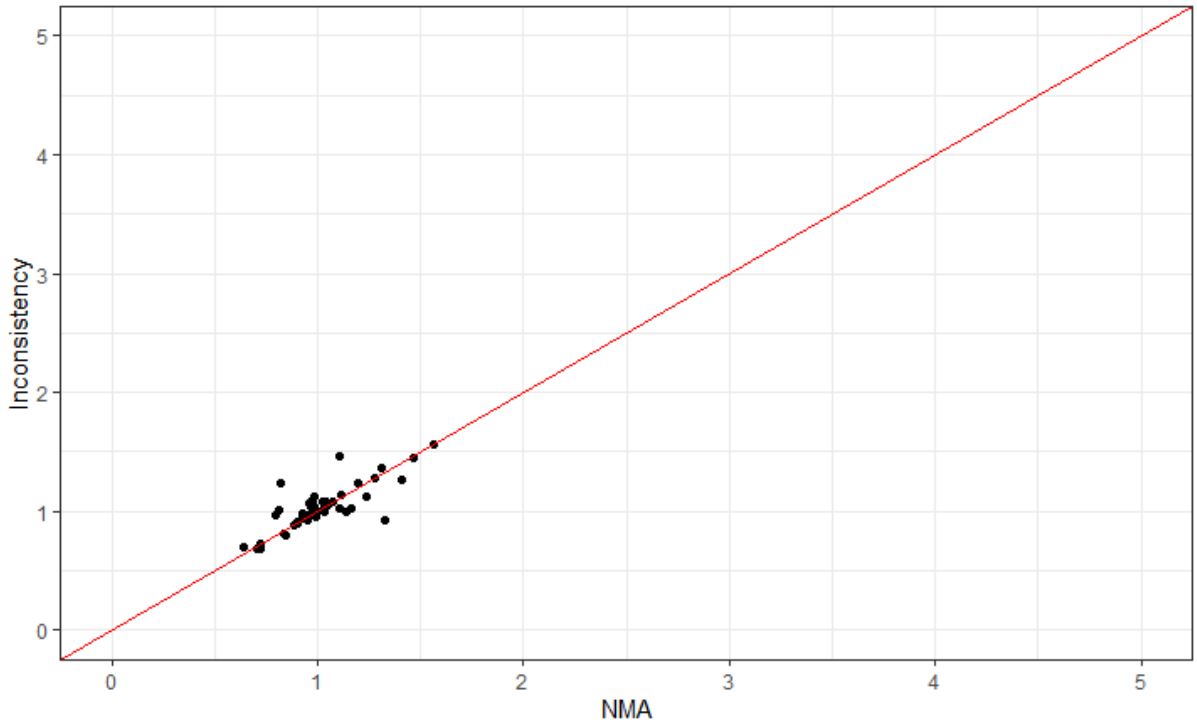
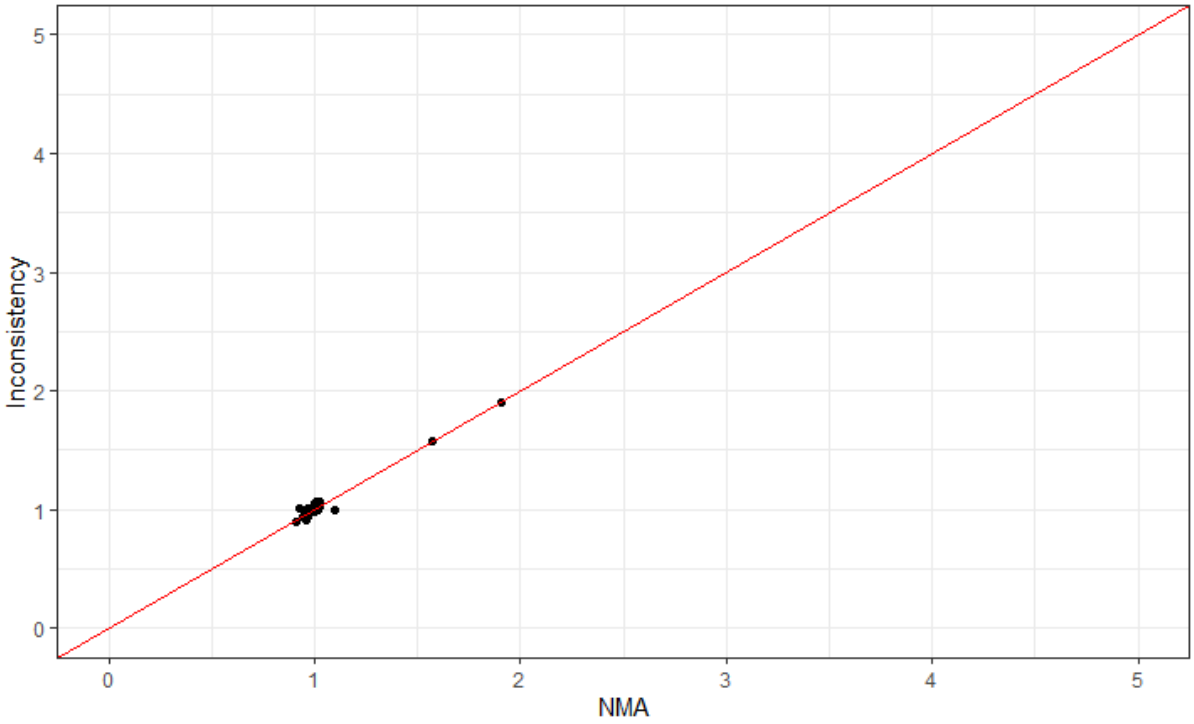


Figure 4: Deviance contributions for the random effect consistency and inconsistency model for nocturnal hypoglycaemia



Results

Change in HbA1c

Figure 5: Network diagram of the network of studies underlying the change in HbA1c NMA with the number of trials for each comparison. Thickness of line indicates number of studies included.

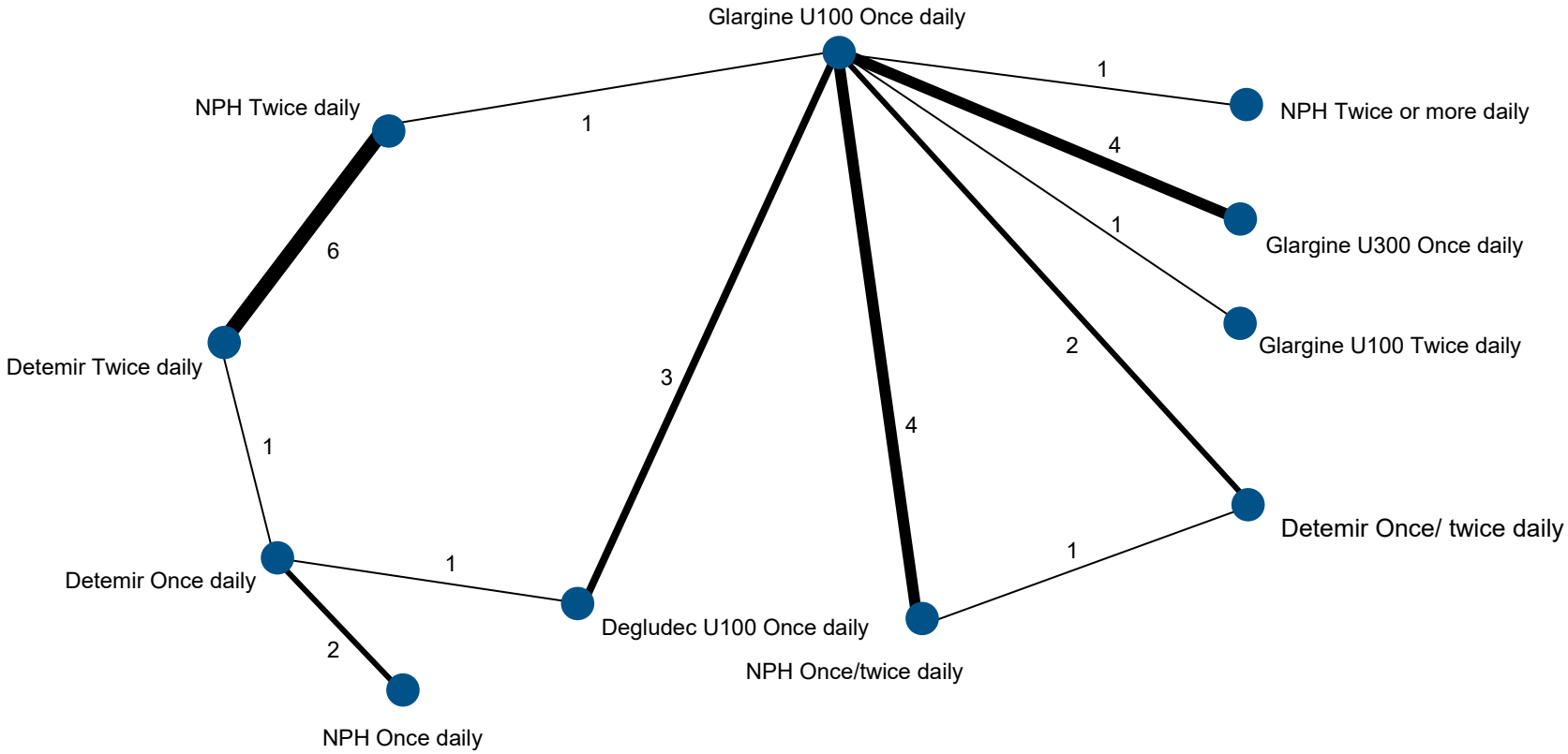


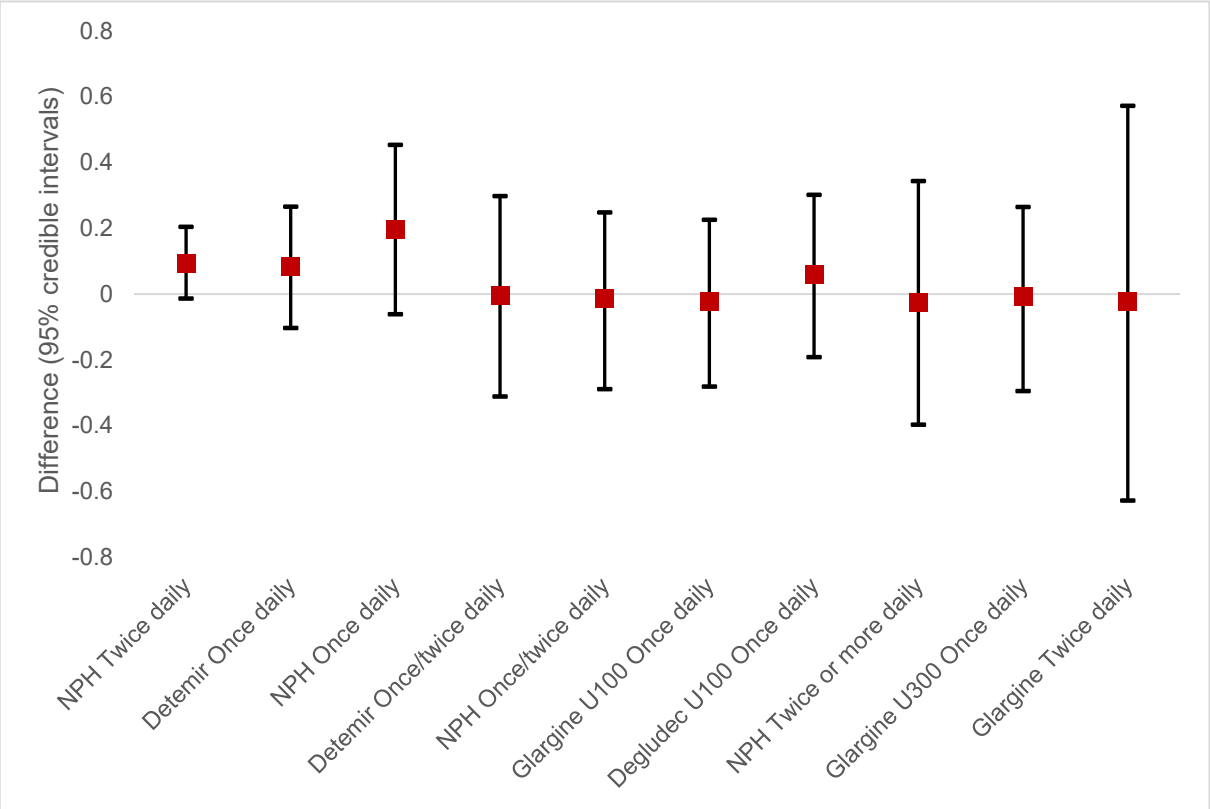
Table 7: Relative effectiveness of all pairwise comparisons

	Pairwise analysis										
NMA		**Detemir twice daily**	**NPH twice daily**	**Detemir once daily**	**NPH once daily**	**Detemir once/twice daily**	**NPH once/twice daily**	**Glargine U100 once daily**	**Degludec U100 once daily**	**NPH twice or more daily**	**Glargine U300 once daily**	**Glargine twice daily**
	Detemir twice daily		-0.09 (-0.18, 0.01)	-0.10 (-0.24, 0.04)								
	NPH twice daily	0.09 (-0.01, 0.20)						0.19 (-0.17, 0.55)				
	Detemir once daily	0.08 (-0.10, 0.27)	-0.01 (-0.22, 0.19)		-0.12 (-0.25, 0.02)				0.00 (-0.18, 0.18)			
	NPH once daily	0.20 (-0.06, 0.45)	0.10 (-0.17, 0.37)	0.11 (-0.06, 0.29)								
	Detemir once/twice daily	0.00 (-0.31, 0.30)	-0.10 (-0.41, 0.21)	-0.09 (-0.37, 0.20)	-0.20 (-0.53, 0.13)		0.30 (-0.35, 0.95)	0.00 (-0.14, 0.14)				
	NPH once/twice daily	-0.01 (-0.29, 0.25)	-0.11 (-0.39, 0.15)	-0.10 (-0.35, 0.15)	-0.21 (-0.52, 0.09)	-0.01 (-0.20, 0.17)		0.01 (-0.10, 0.13)				
	Glargine U100 once daily	-0.02 (-0.28, 0.23)	0.12 (-0.38, 0.13)	-0.10 (-0.34, 0.12)	0.22 (0.51, 0.07)	-0.02 (-0.19, 0.15)	-0.01 (-0.10, 0.09)		-0.07 (-0.17, 0.03)	0.00 (-0.23, 0.23)	-0.02 (-0.11, 0.06)	0.00 (-0.53, 0.53)
	Degludec U100 once daily	0.06 (-0.19, 0.30)	-0.04 (-0.29, 0.21)	-0.02 (-0.23, 0.18)	-0.14 (-0.41, 0.13)	0.06 (-0.15, 0.27)	0.07 (-0.08, 0.23)	0.08 (-0.05, 0.21)				
	NPH twice or more daily	-0.02 (-0.40, 0.34)	-0.12 (-0.49, 0.25)	-0.11 (-0.46, 0.25)	-0.22 (-0.62, 0.17)	-0.02 (-0.34, 0.30)	-0.01 (-0.30, 0.28)	0.00 (-0.28, 0.27)	-0.08 (-0.39, 0.22)			
	Glargine U300 once daily	-0.01 (-0.29, 0.26)	-0.10 (-0.39, 0.17)	-0.09 (-0.35, 0.16)	-0.21 (-0.52, 0.10)	0.00 (-0.21, 0.20)	0.01 (-0.14, 0.15)	0.01 (-0.10, 0.13)	-0.07 (-0.24, 0.10)	0.02 (-0.28, 0.31)		
	Glargine twice daily	-0.02 (-0.63, 0.57)	0.12 (-0.72, 0.48)	-0.10 (-0.70, 0.48)	-0.22 (-0.84, 0.39)	-0.02 (-0.59, 0.55)	-0.01 (-0.56, 0.54)	0.00 (-0.54, 0.54)	-0.08 (-0.64, 0.48)	0.00 (-0.28, 0.31)	-0.01 (-0.57, 0.54)	

The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. Change in HbA1c (%) expressed as mean difference (MD). MD of less than 0 favours row defining treatment. The upper diagonal segment of the chart gives pooled direct evidence, where available. Numbers in parentheses are 95% confidence intervals.MD of less than 0 favours row defining treatment.

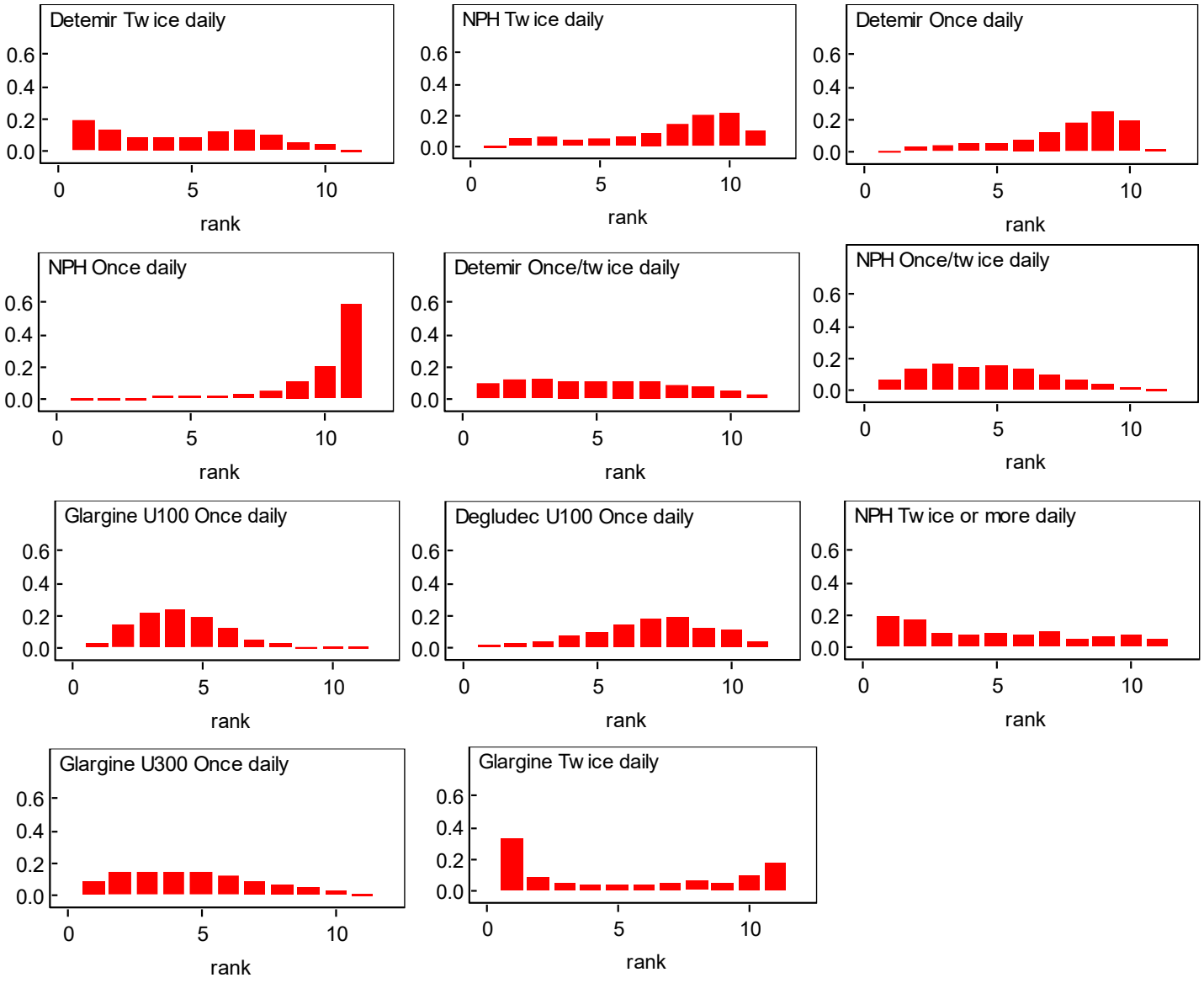
Significant results are in bold.

Figure 6: Caterpillar plot of relative effectiveness of all treatment options versus detemir twice daily



Rank probability histograms

Figure 7: Rank probability histograms (Rank 1= Best)



All hypoglycaemia

Figure 8: Network diagram of the network of studies underlying the all hypoglycaemia NMA with the number of trials for each comparison. Thickness of line indicates number of studies included.

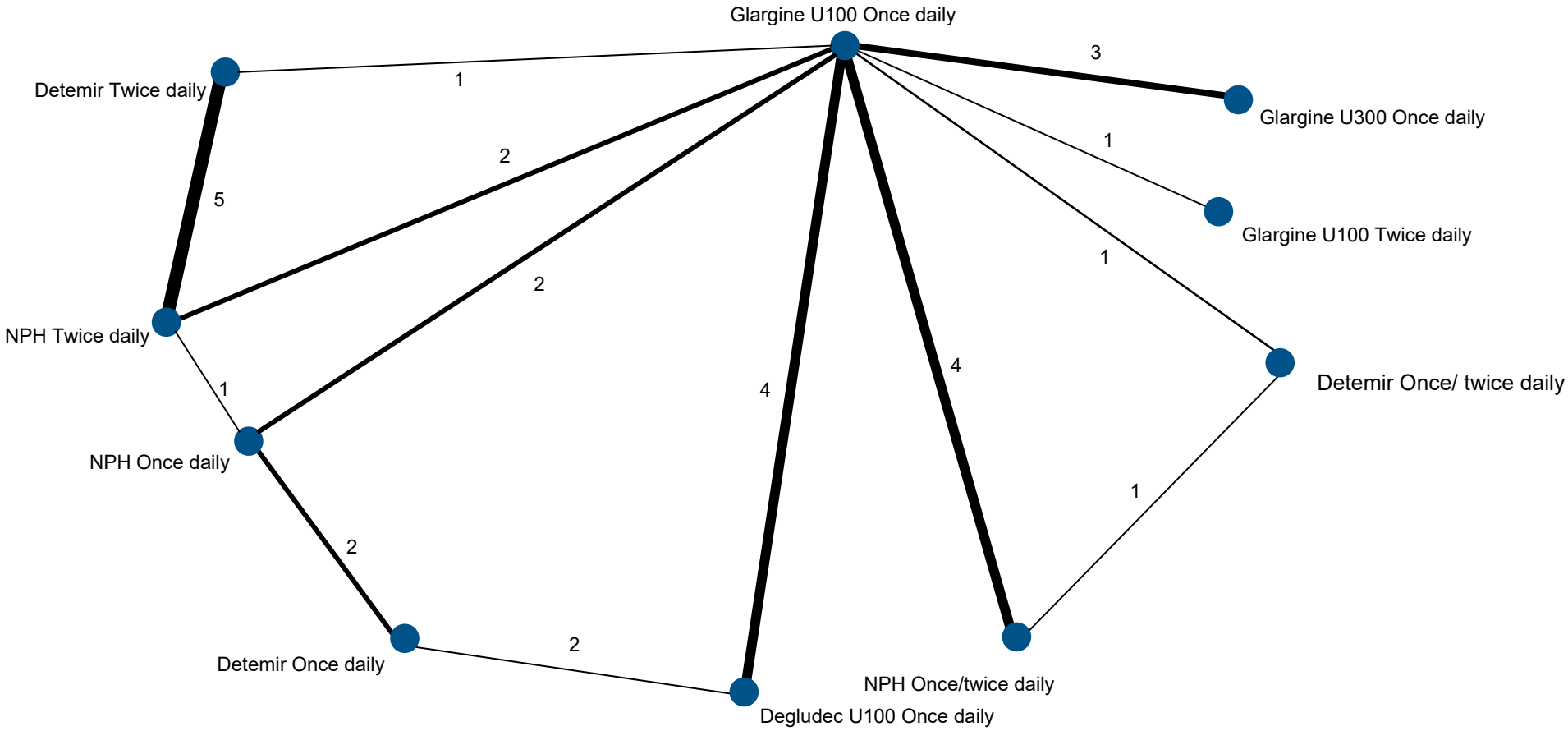


Table 8: Relative effectiveness of all pairwise comparisons

	Pairwise analysis										
NMA		**Detemir twice daily**	**NPH twice daily**	**Glargine U100 once daily**	**Detemir once daily**	**NPH once daily**	**Detemir once/twice daily**	**NPH once/twice daily**	**Degludec U100 once daily**	**Glargine U300 once daily**	**Glargine U100 twice daily**
	Detemir twice daily		**0.81 (0.71, 0.93)**	0.94 (0.87, 1.01)							
	NPH twice daily	1.16 (0.94, 1.43)		**0.66 (0.52, 0.84)/** 0.92 (0.76,1.12) *		0.86 (0.71, 1.05) *					
	Glargine U100 once daily	1.36 (0.98, 1.91)	1.17 (0.85, 1.62)			**1.15 (1.08, 1.22)** / 0.94 (0.81, 1.08) *	**1.05 (1.02, 1.08)**	0.77 (0.44, 1.35)/ 1.05 (1.00, 1.11) *	1.07 (0.94, 1.22)	1.04 (0.82, 1.32)/ 0.97 (0.92, 1.02) *	1.01 (0.83, 1.23)
	Detemir once daily	1.12 (0.71, 1.77)	0.96 (0.62, 1.50)	0.82 (0.59, 1.14)		0.85 (0.65, 1.10)			0.97 (0.93, 1.01)		
	NPH once daily	1.39 (0.91, 2.16)	1.19 (0.80, 1.82)	1.02 (0.75, 1.40)	1.24 (0.93, 1.68)						
	Detemir once/twice daily	1.17 (0.72, 1.93)	1.01 (0.62, 1.64)	0.86 (0.60, 1.24)	1.05 (0.64, 1.71)	0.84 (0.52, 1.35)		**0.71 (0.69, 0.73)**			
	NPH once/twice daily	1.48 (0.98, 2.24)	1.27 (0.85, 1.91)	1.09 (0.84, 1.39)	1.33 (0.87, 1.99)	1.07 (0.71, 1.57)	1.27 (0.88, 1.81)				
	Degludec U100 once daily	1.25 (0.84, 1.87)	1.07 (0.74, 1.59)	0.92 (0.73, 1.15)	1.12 (0.83, 1.51)	0.90 (0.64, 1.25)	1.07 (0.70, 1.65)	0.84 (0.61, 1.19)			
	Glargine U300 once daily	1.37 (0.89, 2.15)	1.18 (0.78, 1.83)	1.01 (0.76, 1.35)	1.23 (0.80, 1.90)	0.99 (0.65, 1.51)	1.17 (0.74, 1.88)	0.93 (0.64, 1.37)	1.10 (0.76, 1.59)		
	Glargine U100 twice daily	1.35 (0.73, 2.52)	1.16 (0.63, 2.15)	0.99 (0.59, 1.67)	1.21 (0.65, 2.24)	0.97 (0.53, 1.78)	1.15 (0.61, 2.18)	0.91 (0.51, 1.63)	1.08 (0.61, 1.90)	0.98 (0.54, 1.78)	

The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. Hazard Ratio (HR) of less than 1 favours row defining treatment. The upper diagonal segment of the chart gives pooled direct evidence, where available. Data presented as rate and risk ratio. RR of less than 1 favours row defining treatment. Numbers in parentheses are 95% confidence intervals.

** Data in blue highlights risk ratio pairwise analysis.*

Significant results are in bold.

Figure 9: Caterpillar plot of relative effectiveness of all treatment options versus detemir twice daily

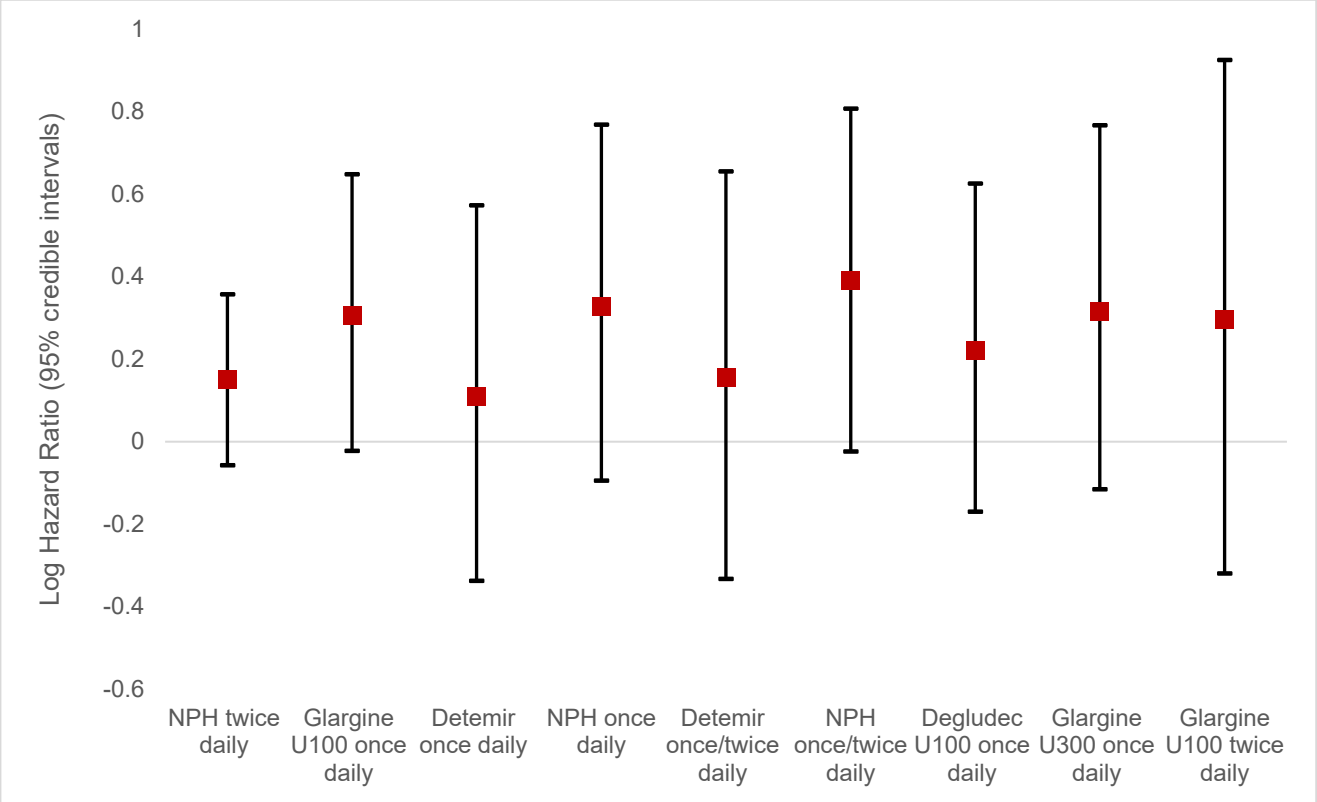
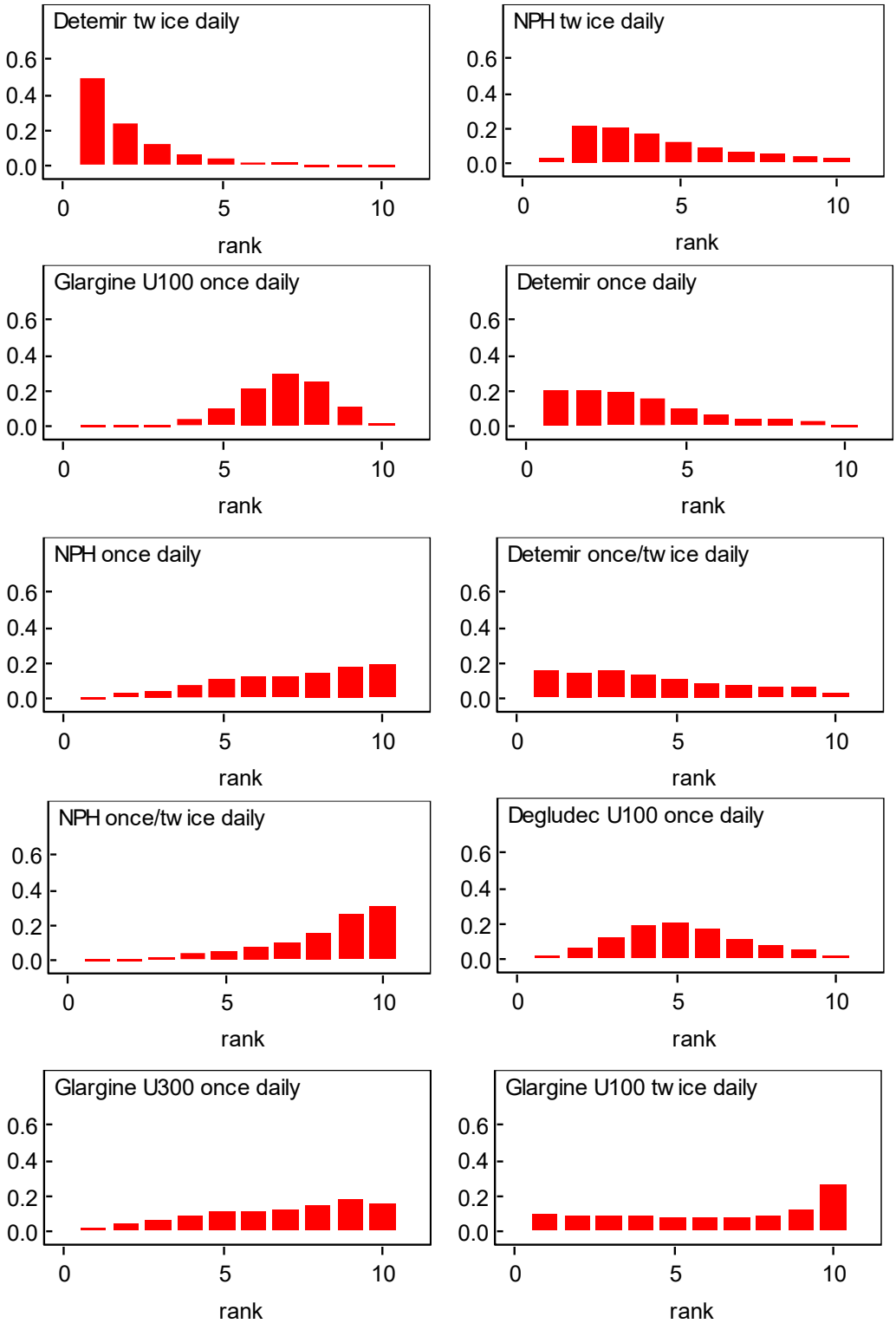


Figure 10: Rank probability histograms (Rank 1= Best)



Severe/Major hypoglycaemia

Figure 11: Network diagram of the network of studies underlying the severe hypoglycaemia NMA with the number of trials for each comparison. Thickness of line indicates number of studies included.

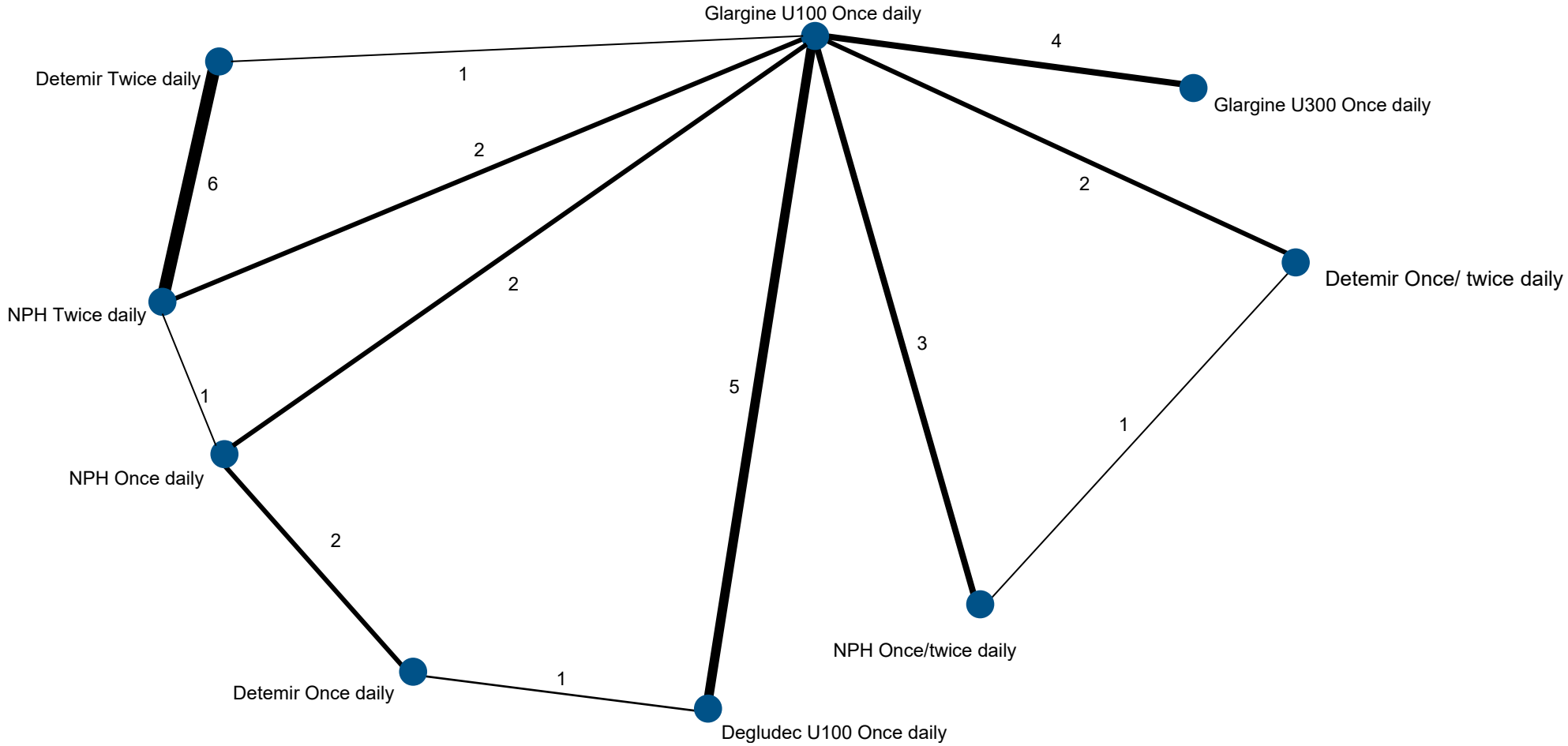


Table 9: Relative effectiveness of all pairwise comparisons

	Pairwise analysis									
NMA		**Detemir twice daily**	**NPH twice daily**	**Glargine U100 once daily**	**Detemir once daily**	**NPH once daily**	**Detemir once/twice daily**	**NPH once/twice daily**	**Degludec U100 once daily**	**Glargine U300 once daily**
	Detemir twice daily		1.01 (0.62, 1.65)/ 0.65 (0.40, 1.08) *	**0.26 (0.09, 0.80)**						
	NPH twice daily	1.14 (0.73, 1.78)		0.78 (0.05, 12.48)/ 0.91 (0.27, 3.37) *		1.67 (0.29, 9.62)				
	Glargine U100 once daily	2.15 (0.78, 6.23)	1.89 (0.68, 5.49)			0.88 (0.68, 1.13)/ 1.85 (0.40, 8.60) *	0.75 (0.55, 1.03)/ 2.50 (0.81, 7.67) *	0.84 (0.28, 2.52)/ 0.71 (0.46, 1.09) *	1.13 (0.94, 1.37)	**0.61 (0.45, 0.82)**/ 1.06 (0.57, 1.99) *
	Detemir once daily	1.89 (0.50, 6.83)	1.66 (0.44, 6.01)	0.88 (0.37, 1.94)		0.72 (0.24, 2.11)			0.81 (0.51, 1.30)	
	NPH once daily	2.25 (0.66, 7.53)	1.98 (0.58, 6.63)	1.05 (0.50, 2.08)	1.19 (0.59, 2.48)					
	Detemir once/twice daily	1.49 (0.43, 5.05)	1.31 (0.37, 4.47)	0.69 (0.34, 1.31)	0.79 (0.28, 2.30)	0.66 (0.25, 1.74)		**0.31 (0.25, 0.38)**		
	NPH once/twice daily	**3.28 (1.00, 10.77)**	2.88 (0.87, 9.54)	1.52 (0.85, 2.64)	1.73 (0.65, 4.85)	1.45 (0.59, 3.65)	**2.21 (1.10, 4.50)**			
	Degludec U100 once daily	1.87 (0.60, 6.03)	1.65 (0.52, 5.30)	0.87 (0.52, 1.44)	0.99 (0.46, 2.33)	0.83 (0.39, 1.88)	1.26 (0.56, 2.98)	0.57 (0.27, 1.24)		
	Glargine U300 once daily	3.01 (0.90, 10.19)	2.65 (0.79, 8.94)	1.40 (0.75, 2.53)	1.60 (0.58, 4.59)	1.34 (0.53, 3.45)	2.03 (0.84, 5.02)	0.92 (0.40, 2.10)	1.61 (0.72, 3.51)	

The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. Hazard Ratio (HR) of less than 1 favours row defining treatment. The upper diagonal segment of the chart gives pooled direct evidence, where available. Data presented as rate and risk ratio. RR of less than 1 favours row defining treatment. Numbers in parentheses are 95% confidence intervals.

** Data in blue highlights risk ratio pairwise analysis.*

Significant results are in bold.

Figure 12: Caterpillar plot of relative effectiveness of all treatment options versus detemir twice daily

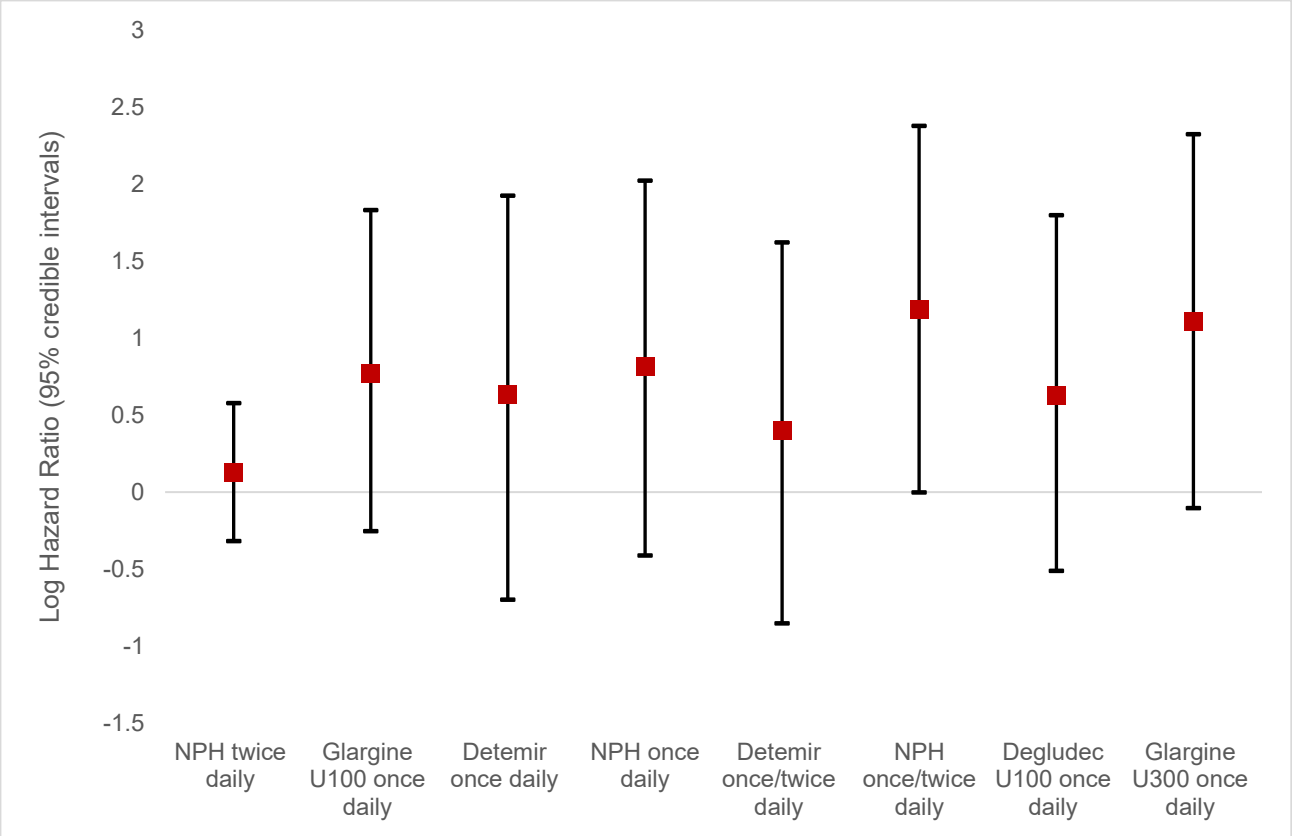
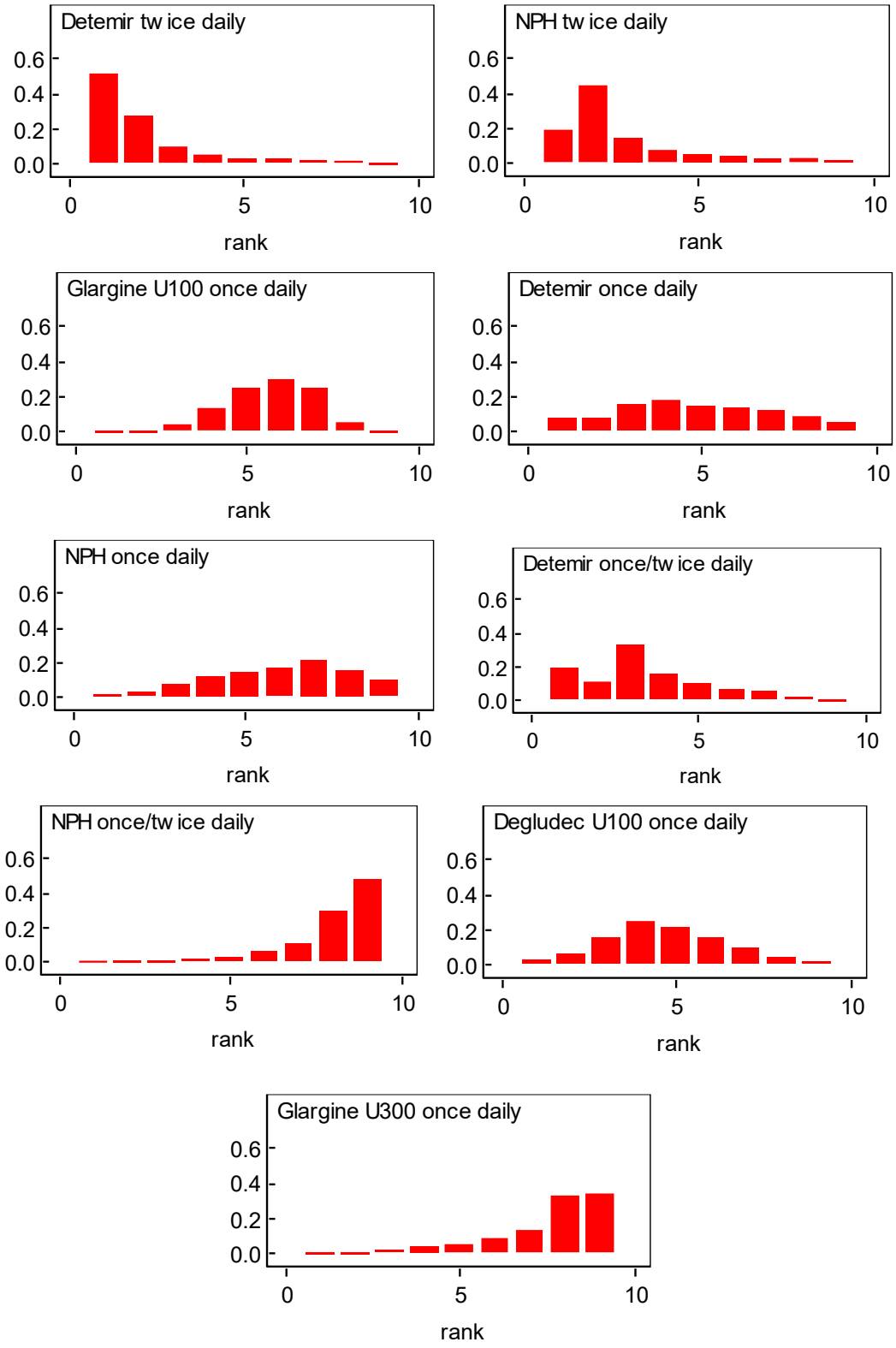


Figure 13: Rank probability histograms (Rank 1= Best)



Nocturnal hypoglycaemia

Figure 14: Network diagram of the network of studies underlying the nocturnal hypoglycaemia NMA with the number of trials for each comparison. Thickness of line indicates number of studies included.

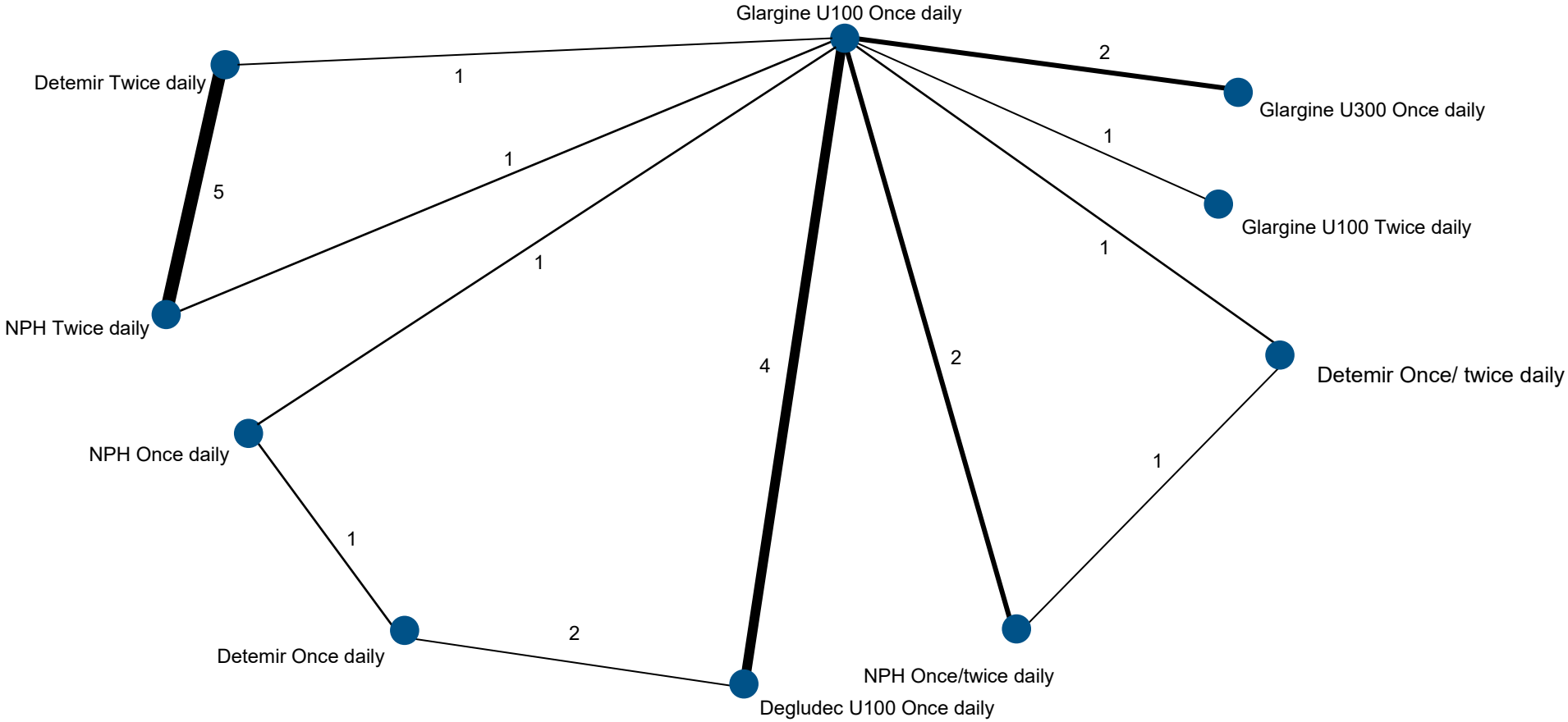


Table 10: Relative effectiveness of all pairwise comparisons

	Pairwise analysis										
NMA		**Detemir twice daily**	**NPH twice daily**	**Glargine U100 once daily**	**Detemir once daily**	**NPH once daily**	**Detemir once/twice daily**	**NPH once/twice daily**	**Degludec U100 once daily**	**Glargine U300 once daily**	**Glargine U100 twice daily**
	Detemir twice daily		**0.75 (0.62, 0.92)**	**0.75 (0.61, 0.92)**							
	NPH twice daily	**1.39 (1.04, 1.89)**		1.87 (0.81, 4.32)							
	Glargine U100 once daily	1.14 (0.62, 1.99)	0.82 (0.43, 1.47)			**0.77 (0.67, 0.88)**	**0.81 (0.75, 0.87)**	**1.12 (1.02, 1.23)**	**1.45 (1.23, 1.70)**	**1.13 (1.00, 1.28)**	1.78 (0.83, 3.86)
	Detemir once daily	1.54 (0.71, 3.31)	1.11 (0.50, 2.42)	1.34 (0.82, 2.31)		**0.75 (0.69, 0.82)**			2.53 (0.87, 7.41)		
	NPH once daily	1.75 (0.78, 3.77)	1.26 (0.55, 2.77)	1.53 (0.91, 2.65)	1.14 (0.66, 1.91)						
	Detemir once/twice daily	1.07 (0.48, 2.25)	0.77 (0.33, 1.65)	0.93 (0.56, 1.55)	0.69 (0.32, 1.39)	0.61 (0.29, 1.26)		**0.68 (0.64, 0.73)**			
	NPH once/twice daily	1.18 (0.56, 2.37)	0.85 (0.39, 1.74)	1.03 (0.67, 1.58)	0.77 (0.38, 1.46)	0.68 (0.33, 1.33)	1.11 (0.66, 1.85)				
	Degludec U100 once daily	0.74 (0.37, 1.40)	0.54 (0.26, 1.03)	**0.65 (0.47, 0.89)**	**0.49 (0.30, 0.74)**	**0.43 (0.24, 0.73)**	0.70 (0.38, 1.28)	0.63 (0.37, 1.08)			
	Glargine U300 once daily	1.01 (0.47, 2.08)	0.73 (0.33, 1.53)	0.89 (0.56, 1.42)	0.66 (0.32, 1.28)	0.58 (0.28, 1.17)	0.95 (0.48, 1.92)	0.86 (0.46, 1.63)	1.36 (0.78, 2.41)		
	Glargine U100 twice daily	0.63 (0.19, 1.99)	0.45 (0.13, 1.44)	0.55 (0.20, 1.51)	0.41 (0.13, 1.24)	0.36 (0.11, 1.11)	0.59 (0.19, 1.83)	0.53 (0.18, 1.60)	0.85 (0.29, 2.44)	0.62 (0.20, 1.88)	

The lower diagonal segment of the chart is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects. The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. Odds Ratio (OR) of less than 1 favours row defining treatment. The upper diagonal segment of the chart gives pooled direct evidence, where available. Numbers in parentheses are 95% confidence intervals. Odds Ratio (OR) of less than 1 favours row defining treatment.

Significant results are in bold.

Figure 15: Caterpillar plot of relative effectiveness of all treatment options versus detemir twice daily

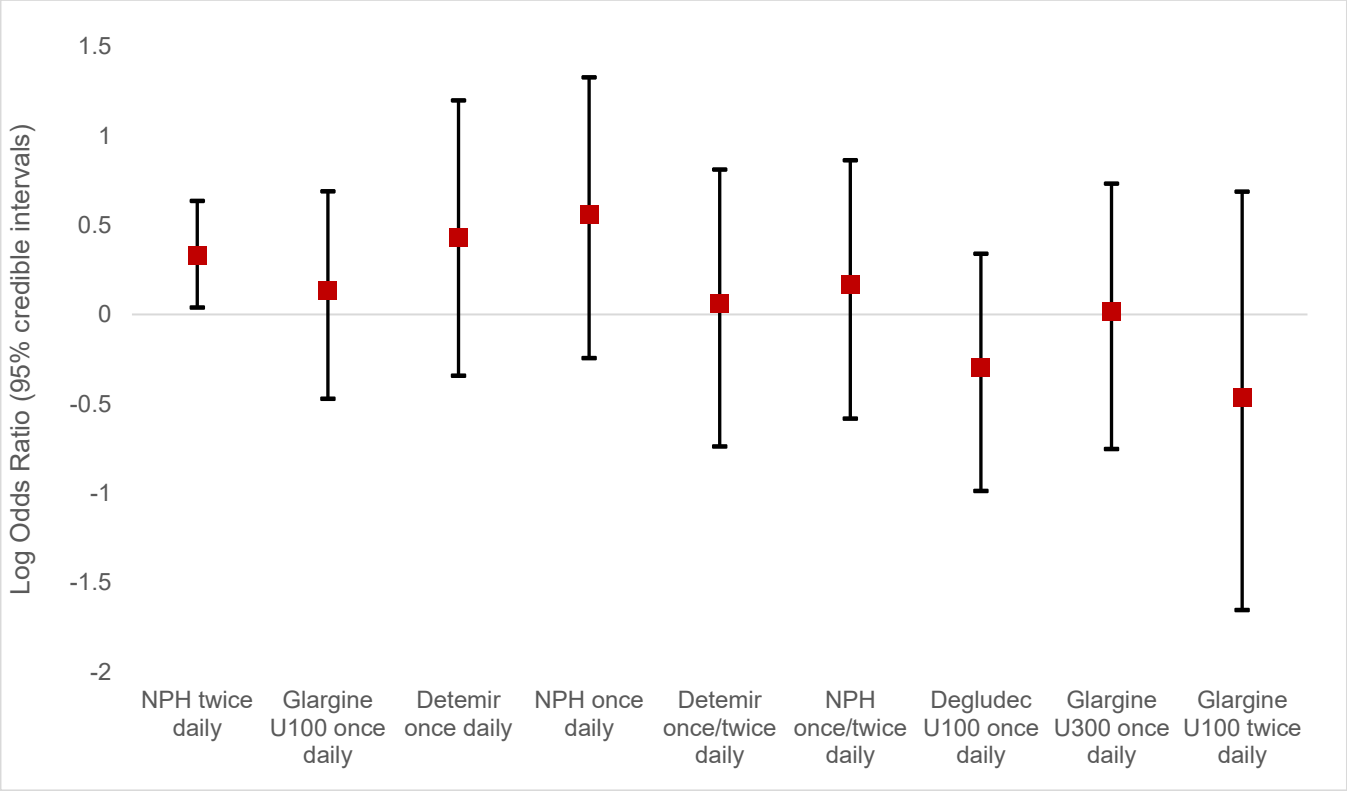
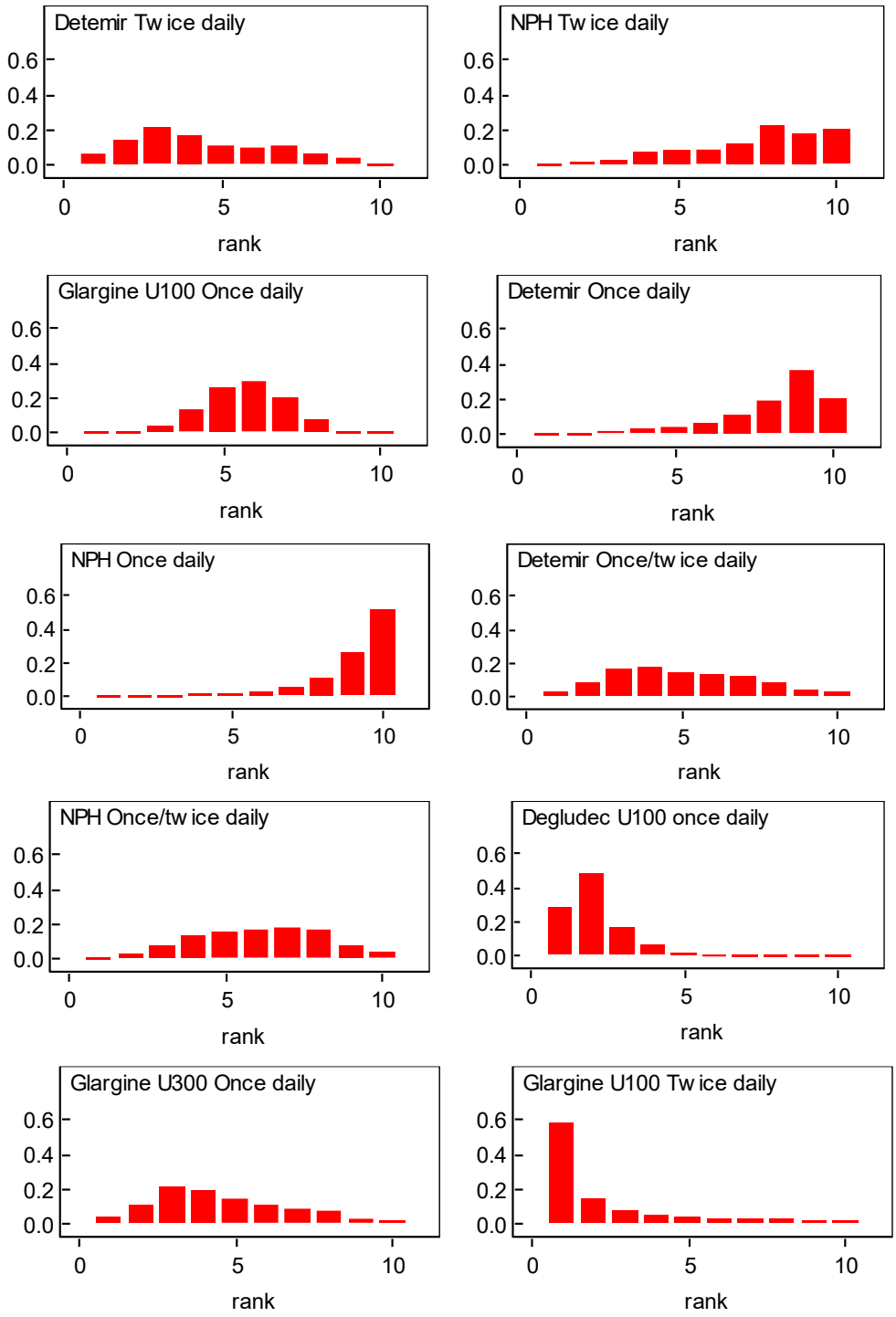


Figure 16: Rank probability histograms (Rank 1= Best)



Winbugs code

HbA1c Fixed effects model

```
# Normal likelihood, identity link
# Fixed effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
    for (k in 1:na[i]) {                #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)    # calculate variances
        prec[i,k] <- 1/var[i,k]       # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {              # LOOP THROUGH ARMS
# mean of LOR distributions, with multi-arm trial correction
        delta[i,k] <-  d[t[i,k]] - d[t[i,1]]
      }
  }
# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
          rk[k]<-rank(d[],k)
best[k]<-equals(rank(d[],k),1)}
totresdev <- sum(resdev[])             #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
for (c in 1:(nt-1))
{  for (k in (c+1):nt)
{  D[c,k] <- d[k] - d[c]}}
}                                       # *** PROGRAM ENDS
```

HbA1c Random effects model

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
    for (k in 1:na[i]) {                #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)    # calculate variances
        prec[i,k] <- 1/var[i,k]       # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
```

```
    for (k in 2:na[i]) {              # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
          rk[k]<-rank(d[],k)
best[k]<-equals(rank(d[],k),1)}
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)      # vague prior for between-trial SD
tau <- pow(sd,-2)    # between-trial precision = (1/between-trial variance)
for (c in 1:(nt-1))
{  for (k in (c+1):nt)
{  D[c,k] <- d[k] - d[c]}}
 }                                    # *** PROGRAM ENDS
```

All hypoglycaemia Fixed effects model

```
model {
for(i in 1:NumStudiesC) {    # indexes studies with cloglog data
  mu[i] ~ dnorm(0, .0001)    # vague priors for all trial baselines
  for (j in 1:na[i]) {       # indexes arms
    k[i,j] ~ dbin(p[i,j],n[i,j])    # binomial likelihood
# model for linear predictor
#    cloglog(p[i,j]) <- log(time[i]/1) + mu[i] + d[t[i,j]] - d[t[i,1]]
    eta[i,j] <- log(time[i]) + mu[i] + d[t[i,j]] - d[t[i,1]]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras(2009, Chapter 7)
    cloglog(p[i,j]) <- eta[i,j]*(1-step(-xi1-eta[i,j]))*(1-step(eta[i,j]-
xi2))
       -xi1*step(-xi1-eta[i,j])+ xi2*step(eta[i,j]-xi2)
    rhat[i,j] <- p[i,j] * n[i,j] # expected value of the numerators
# deviance contribution
    dev[i,j] <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
            + (n[i,j]-k[i,j]) * (log(n[i,j]-k[i,j]) - log(n[i,j]-
rhat[i,j])))
    }                          # close arm loop
  resdev[i] <- sum(dev[i,1:na[i]]) # summed deviance contribution
  }                            # close study loop
for(i in 1:NumStudiesP) {    # indexes studies with poisson data
  mu[i + NumStudiesC] ~ dnorm(0, .0001) # vague priors for all trial
baselines
  for (j in 1:naP[i]) {      # indexes arms
    r[i,j] ~  dpois(theta[i,j]) # Poisson likelihood
    theta[i,j] <- lambda[i,j] * E[i,j] # failure rate * exposure
# model for linear predictor
    log(lambda[i,j]) <- mu[i + NumStudiesC] + d[tP[i,j]] - d[tP[i,1]]
# deviance contribution
```

```
    dev[i + NumStudiesC,j] <- 2*((theta[i,j]-r[i,j]) + r[i,j] * log(r[i,j]
/ theta[i,j]))
    }                          # close arm loop
# summed deviance contribution
  resdev[i + NumStudiesC] <- sum(dev[i + NumStudiesC,1:naP[i]])
  }                            # close study loop
totresdev <- sum(resdev[])     # total residual deviance
d[1]<-0                        # effect is 0 for reference treatment
for (j in 2:nt) {              # indexes treatments
  d[j] ~ dnorm(0, .0001)       # vague priors for treatment effects
  }                            # close treatment loop
# cloglog truncation values
xi1 <- 10
xi2 <- 3
# pairwise HRs and LHRs for all possible pairwise comparisons
for (c in 1:(nt-1)) {
  for (j in (c+1):nt) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
    }
  }
# ranking on relative scale
for (j in 1:nt) {
  rk[j]       <- nt+1-rank(d[],j)
  best[j]     <- equals(rk[j],1) # probability that treat j is best
  for (h in 1:nt) {
    pRk[h,j]  <- equals(rk[j],h) # probability that treat j is hth best
    }
  }
}
```

All hypoglycaemia Random effects model

```
model {
for(i in 1:NumStudiesC) {                    # indexes studies with cloglog data
  mu[i] ~ dnorm(0, .0001)                    # vague priors for all trial baselines
 delta[i,1] <- 0                    # effect is zero for control arm
 w[i,1]    <- 0                     # multi-arm adjustment = zero for ctrl
  for (j in 1:na[i]) {                       # indexes arms
   k[i,j]       ~ dbin(p[i,j],n[i,j])        # binomial likelihood
    eta[i,j] <- log(time[i]) + mu[i] + delta[i,j]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras(2009, Chapter 7)
    cloglog(p[i,j]) <- eta[i,j]*(1-step(-xi1-eta[i,j]))*(1-step(eta[i,j]-
xi2))
        -xi1*step(-xi1-eta[i,j])+ xi2*step(eta[i,j]-xi2)
   rhat[i,j]      <- p[i,j] * n[i,j]           # expected value of the numerators
   dev[i,j]       <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                  + (n[i,j]-k[i,j]) * (log(n[i,j]-k[i,j])
                  - log(n[i,j]-rhat[i,j])))    # deviance contribution
   }                                         # close arm loop
 for (j in 2:na[i]) {                  # indexes arms
   delta[i,j]  ~  dnorm(md[i,j],taud[i,j])        # trial-specific LHR distributions
   md[i,j]     <- d[t[i,j]] - d[t[i,1]] + sw[i,j]
                                         # mean of LHR distributions (with
                                         # multi-arm trial correction)
   taud[i,j]   <- tau *2*(j-1)/j               # precision of LOR distributions (with
                                         # multi-arm trial correction)
   w[i,j]      <- (delta[i,j] - d[t[i,j]] + d[t[i,1]])
                                         # adjustment for multi-arm RCTs
   sw[i,j]     <- sum(w[i,1:j-1])/(j-1)
                                         # cumulative adjustment for multi-arm
                                         # trials
}
```

```
  resdev[i] <- sum(dev[i,1:na[i]])            # summed deviance contribution
  }                                           # close study loop

for(i in 1:NumStudiesP) {                     # indexes studies with poisson data
  mu[i + NumStudiesC] ~ dnorm(0, .0001)           # vague priors for all trial baselines
 delta[i + NumStudiesC,1] <- 0                # effect is zero for control arm
 w[i + NumStudiesC,1]     <- 0                # multi-arm adjustment = zero for ctrl
  for (j in 1:naP[i]) {                       # indexes arms
    r[i,j] ~  dpois(theta[i,j])                   # Poisson likelihood
    theta[i,j] <- lambda[i,j] * E[i,j]            # failure rate * exposure
    log(lambda[i,j]) <- mu[i + NumStudiesC] + delta[i + NumStudiesC,j]   # model for linear predictor

    dev[i + NumStudiesC,j] <- 2 * ((theta[i,j]-r[i,j]) + r[i,j] * log(r[i,j] / theta[i,j]))
                                              # deviance contribution
    }                                         # close arm loop
  for (j in 2:naP[i]) {                       # indexes arms
    delta[i + NumStudiesC,j] ~  dnorm(md[i + NumStudiesC,j],taud[i + NumStudiesC,j])
                                              # trial-specific LHR distributions
    md[i + NumStudiesC,j]    <- d[tP[i,j]] - d[tP[i,1]]
                          + sw[i + NumStudiesC,j] # mean of LHR distributions (with
                                              # multi-arm trial correction)
    taud[i + NumStudiesC,j]  <- tau *2*(j-1)/j      # precision of LOR distributions (with
                                              # multi-arm trial correction)
    w[i + NumStudiesC,j]     <- (delta[i + NumStudiesC,j] - d[tP[i,j]] + d[tP[i,1]])
                                              # adjustment for multi-arm RCTs
    sw[i + NumStudiesC,j]    <- sum(w[i + NumStudiesC,1:j-1])/(j-1)
                                              # cumulative adjustment for multi-arm trials
}
  resdev[i + NumStudiesC] <- sum(dev[i + NumStudiesC,1:naP[i]])
                                              # summed deviance contribution
  }                                           # close study loop

totresdev     <- sum(resdev[])                    # total residual deviance

d[1]<-0                                       # effect is 0 for reference treatment
for (j in 2:nt) {                             # indexes treatments
  d[j] ~ dnorm(0, .0001)                          # vague priors for treatment effects
      }                                   # close treatment loop

sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)


# cloglog truncation values
xi1 <- 10
xi2 <- 3

# pairwise HRs and LHRs for all possible pairwise comparisons
for (c in 1:(nt-1)) {
  for (j in (c+1):nt) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
    }
  }

# ranking on relative scale
for (j in 1:nt) {
  rk[j]       <- nt+1-rank(d[],j)
  best[j]     <- equals(rk[j],1)                # probability that treat j is best
  for (h in 1:nt) {
    pRk[h,j]  <- equals(rk[j],h)                # probability that treat j is hth best
    }
  }

}
```

Severe/ major hypoglycaemia fixed effects model

```
model {
for(i in 1:NumStudiesC) {    # indexes studies with cloglog data
  mu[i] ~ dnorm(0, .0001)    # vague priors for all trial baselines
  for (j in 1:na[i]) {       # indexes arms
    k[i,j] ~ dbin(p[i,j],n[i,j])    # binomial likelihood
# model for linear predictor
#    cloglog(p[i,j]) <- log(time[i]/1) + mu[i] + d[t[i,j]] - d[t[i,1]]
    eta[i,j] <- log(time[i]) + mu[i] + d[t[i,j]] - d[t[i,1]]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras(2009, Chapter 7)
    cloglog(p[i,j]) <- eta[i,j]*(1-step(-xi1-eta[i,j]))*(1-step(eta[i,j]-
xi2))
       -xi1*step(-xi1-eta[i,j])+ xi2*step(eta[i,j]-xi2)
    rhat[i,j] <- p[i,j] * n[i,j] # expected value of the numerators
# deviance contribution
    dev[i,j] <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
            + (n[i,j]-k[i,j]) * (log(n[i,j]-k[i,j]) - log(n[i,j]-
rhat[i,j])))
    }                          # close arm loop
  resdev[i] <- sum(dev[i,1:na[i]]) # summed deviance contribution
  }                            # close study loop
for(i in 1:NumStudiesP) {    # indexes studies with poisson data
  mu[i + NumStudiesC] ~ dnorm(0, .0001) # vague priors for all trial
baselines
  for (j in 1:naP[i]) {      # indexes arms
    r[i,j] ~  dpois(theta[i,j]) # Poisson likelihood
    theta[i,j] <- lambda[i,j] * E[i,j] # failure rate * exposure
# model for linear predictor
    log(lambda[i,j]) <- mu[i + NumStudiesC] + d[tP[i,j]] - d[tP[i,1]]
# deviance contribution
    dev[i + NumStudiesC,j] <- 2*((theta[i,j]-r[i,j]) + r[i,j] * log(r[i,j]
/ theta[i,j]))
    }                          # close arm loop
# summed deviance contribution
  resdev[i + NumStudiesC] <- sum(dev[i + NumStudiesC,1:naP[i]])
  }                            # close study loop
totresdev <- sum(resdev[])   # total residual deviance
d[1]<-0                      # effect is 0 for reference treatment
for (j in 2:nt) {            # indexes treatments
  d[j] ~ dnorm(0, .0001)     # vague priors for treatment effects
  }                          # close treatment loop
# cloglog truncation values
xi1 <- 10
xi2 <- 3
# pairwise HRs and LHRs for all possible pairwise comparisons
for (c in 1:(nt-1)) {
  for (j in (c+1):nt) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
    }
  }
# ranking on relative scale
for (j in 1:nt) {
  rk[j]       <- nt+1-rank(d[],j)
  best[j]     <- equals(rk[j],1) # probability that treat j is best
  for (h in 1:nt) {
    pRk[h,j]  <- equals(rk[j],h) # probability that treat j is hth best
    }
  }
}
```

Severe/ major hypoglycaemia random effects model

```
model {
for(i in 1:NumStudiesC) {                    # indexes studies with cloglog data
  mu[i] ~ dnorm(0, .0001)                    # vague priors for all trial baselines
 delta[i,1] <- 0                             # effect is zero for control arm
  w[i,1]    <- 0                             # multi-arm adjustment = zero for ctrl
  for (j in 1:na[i]) {                       # indexes arms
    k[i,j]        ~  dbin(p[i,j],n[i,j])     # binomial likelihood
      eta[i,j] <- log(time[i]) + mu[i] + delta[i,j]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras(2009, Chapter 7)
      cloglog(p[i,j]) <- eta[i,j]*(1-step(-xi1-eta[i,j]))*(1-step(eta[i,j]-
xi2))
          -xi1*step(-xi1-eta[i,j])+ xi2*step(eta[i,j]-xi2)
    rhat[i,j]      <- p[i,j] * n[i,j]          # expected value of the numerators
    dev[i,j]       <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                    + (n[i,j]-k[i,j]) * (log(n[i,j]-k[i,j])
                    - log(n[i,j]-rhat[i,j])))  # deviance contribution
    }                                          # close arm loop
  for (j in 2:na[i]) {                         # indexes arms
    delta[i,j]  ~  dnorm(md[i,j],taud[i,j])    # trial-specific LHR distributions
    md[i,j]     <- d[t[i,j]] - d[t[i,1]] + sw[i,j]
                                               # mean of LHR distributions (with
                                               # multi-arm trial correction)
    taud[i,j]   <- tau *2*(j-1)/j              # precision of LOR distributions (with
                                               # multi-arm trial correction)
    w[i,j]      <- (delta[i,j] - d[t[i,j]] + d[t[i,1]])
                                               # adjustment for multi-arm RCTs
    sw[i,j]     <- sum(w[i,1:j-1])/(j-1)
                                               # cumulative adjustment for multi-arm
                                               # trials
}
  resdev[i] <- sum(dev[i,1:na[i]])             # summed deviance contribution
  }                                            # close study loop

for(i in 1:NumStudiesP) {                      # indexes studies with poisson data
  mu[i + NumStudiesC] ~ dnorm(0, .0001)        # vague priors for all trial baselines
 delta[i + NumStudiesC,1] <- 0                 # effect is zero for control arm
  w[i + NumStudiesC,1]    <- 0                 # multi-arm adjustment = zero for ctrl
  for (j in 1:naP[i]) {                        # indexes arms
    r[i,j] ~  dpois(theta[i,j])                # Poisson likelihood
    theta[i,j] <- lambda[i,j] * E[i,j]         # failure rate * exposure
    log(lambda[i,j]) <- mu[i + NumStudiesC] + delta[i + NumStudiesC,j]   # model for linear predictor

    dev[i + NumStudiesC,j] <- 2 * ((theta[i,j]-r[i,j]) + r[i,j] * log(r[i,j] / theta[i,j]))
                                               # deviance contribution
    }                                          # close arm loop
  for (j in 2:naP[i]) {                        # indexes arms
    delta[i + NumStudiesC,j] ~  dnorm(md[i + NumStudiesC,j],taud[i + NumStudiesC,j])
                                               # trial-specific LHR distributions
    md[i + NumStudiesC,j]    <- d[tP[i,j]] - d[tP[i,1]]
                         + sw[i + NumStudiesC,j] # mean of LHR distributions (with
                                               # multi-arm trial correction)
    taud[i + NumStudiesC,j]  <- tau *2*(j-1)/j      # precision of LOR distributions (with
                                               # multi-arm trial correction)
    w[i + NumStudiesC,j]     <- (delta[i + NumStudiesC,j] - d[tP[i,j]] + d[tP[i,1]])
                                               # adjustment for multi-arm RCTs
    sw[i + NumStudiesC,j]    <- sum(w[i + NumStudiesC,1:j-1])/(j-1)
                                               # cumulative adjustment for multi-arm trials
}
  resdev[i + NumStudiesC] <- sum(dev[i + NumStudiesC,1:naP[i]])
                                               # summed deviance contribution
  }                                            # close study loop

totresdev     <- sum(resdev[])                 # total residual deviance
```

```
d[1]<-0                                  # effect is 0 for reference treatment
for (j in 2:nt) {                        # indexes treatments
  d[j] ~ dnorm(0, .0001)                        # vague priors for treatment effects
      }                                  # close treatment loop

sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)


# cloglog truncation values
xi1 <- 10
xi2 <- 3

# pairwise HRs and LHRs for all possible pairwise comparisons
for (c in 1:(nt-1)) {
  for (j in (c+1):nt) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
    }
  }

# ranking on relative scale
for (j in 1:nt) {
  rk[j]       <- nt+1-rank(d[],j)
  best[j]     <- equals(rk[j],1)              # probability that treat j is best
  for (h in 1:nt) {
    pRk[h,j]  <- equals(rk[j],h)               # probability that treat j is hth best
    }
  }
```

Nocturnal hypoglycaemia fixed effects model

```
# Binomial likelihood, logit link
# Fixed effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # LOOP THROUGH ARMS
 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
 logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear predictor
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
 }
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

for (l in 1:nt) { pbest[l]<-equals(rank(d[],l),5) }

for (z in 1:(nt-1))
{
caterpillar[z] <- exp(d[z+1])-d[1]
}

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}

for (k in 1:nt) {
 rk[k] <- rank(d[],k) # assumes events are "bad"
 best[k] <- equals(rk[k],1) #calculate probability that treat k is best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
 }
```

```
} # *** PROGRAM ENDS
```

Nocturnal hypoglycaemia random effects model

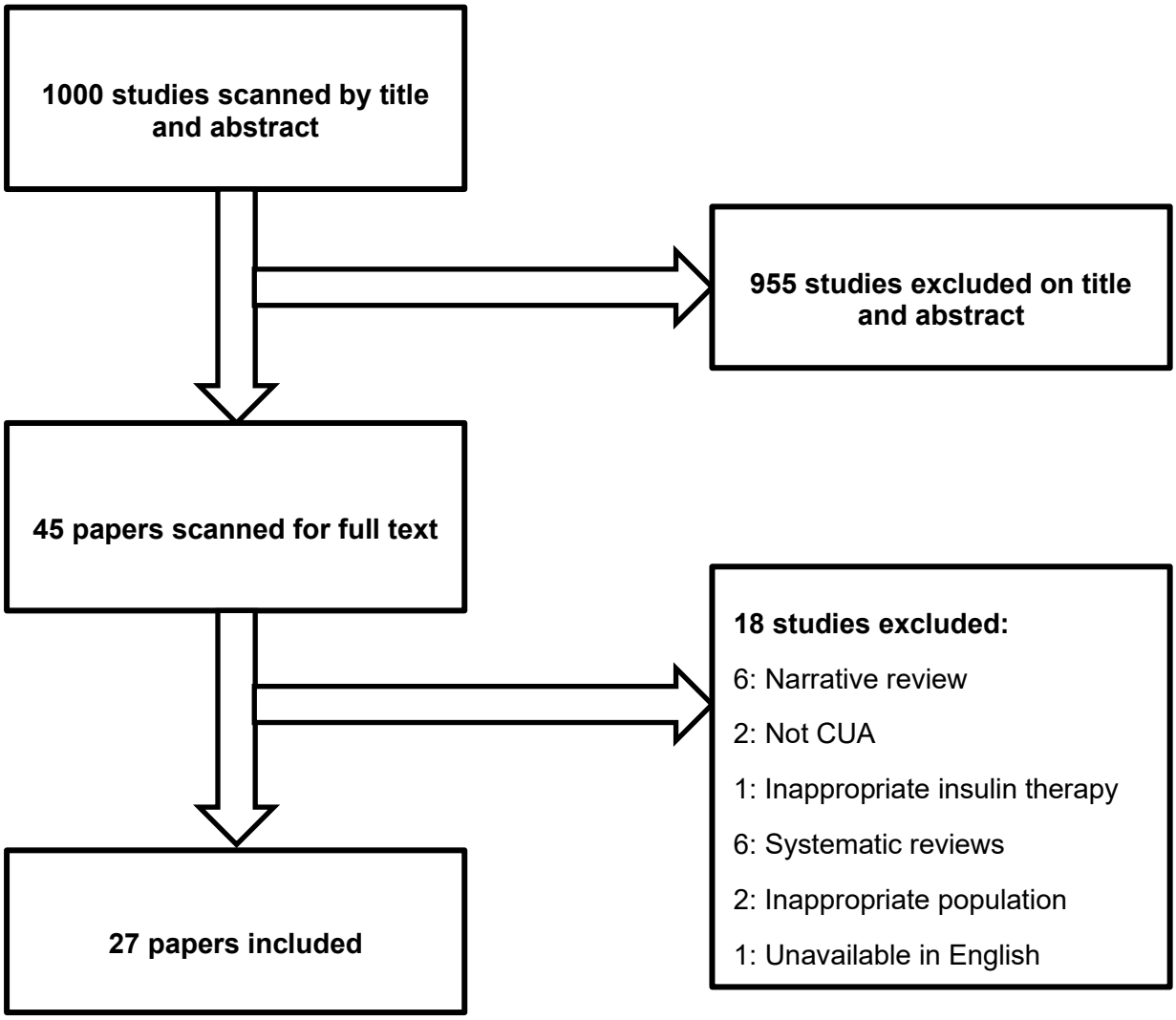
```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
 w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
 delta[i,1] <- 0 # treatment effect is zero for control arm
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # LOOP THROUGH ARMS
 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
 logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
 for (k in 2:na[i]) { # LOOP THROUGH ARMS
 delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
 md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with multi-arm trial correction)
 taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with multi-arm trial correction)
 w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
 sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
 }
 }
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
sd ~ dunif(0,5) # vague prior for between-trial SD. ALTERNATIVES BELOW
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}

for (k in 1:nt) {
 rk[k] <- rank(d[],k) # assumes events are “bad”
 best[k] <- equals(rk[k],1) #calculate probability that treat k is best
 for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
 }


} # *** PROGRAM ENDS
```

Appendix L – Economic evidence study selection



Appendix M – Economic evidence tables

Table 1: Cameron et al (2009)

Cameron et al (2009). Cost-effectiveness of insulin analogues for diabetes mellitus.[1]

Study details

Analysis: Cost utility analysis

Approach to analysis: CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables.

Diabetes related complications considered: Include mild/ moderate and severe hypoglycaemic events, CVD, nephropathy, gangrene, ketoacidosis, cataract, foot ulcer, neuropathy, depression from hypoglycaemic events

Perspective: Canadian third-party payer

Time horizon: 60 years

Discounting: 5%

Interventions

Analysis 1:

Intervention 1: Detemir (dose:0.28 units/kg)

Intervention 2: NPH (dose:0.34 units/kg)

Injection frequency: NR

Analysis 2:

Intervention 1: Glargine (dose:0.28 units/kg)

Intervention 2: NPH (dose:0.34 units/kg)

Injection frequency: NR

Population

Population: Adults with Type 1 Diabetes

Characteristics: NR

Data sources

Resource use: Insulin dosage obtained from endocrinologist member of the Canadian Optimal Medication Prescribing and Utilization Service Expert Review Committee. Unclear as to how resource use for SMGB test/ injections were calculated.

Baseline/natural history: Baseline risk equation used by Palmer et al[2]

Effectiveness: Meta-analysis of randomised control trials conducted by CADTH and Singh et al[3]

Costs: Unit cost of drugs obtained from Ontario Drug Benefit Formulary Comparative Drug Index (June 6, 2007) and the PPS Pharma Buyers Guide, Ontario Edition (July 2007). Cost of diabetes related complication obtained from Ontario Diabetes Economic Model[4], the Alberta Health Costing Project[5] and other published sources[6–8]. All costs inflated to 2007 prices.

QoL: Baseline utility values derived from a catalogue of eq-5d index scores for the United States population. Disutility from hypoglycaemic events sourced from US based population[9]. Disutility from other diabetes related complications obtained from sources primarily using the eq-5d measurement tool (listed in more detail in https://www.cmaj.ca/content/cmaj/suppl/2009/02/10/180.4.400.DC2/cost-cam-1-at.pdf)

Base-case results

2007 Canadian dollars

Analysis	Insulin	Absolute		Incremental		
		Costs (Can$)	QALYs	Costs (Can$)	QALYs	ICER
Analysis 1	NPH	68,370	11.034			
	Detemir	72,714	11.045	4,344	0.011	Can$ 387,729/ QALY
Analysis 2	NPH	67,370	11.097			
	Glargine	70,751	11.136	3,423	0.039	Can$ 87,932 / QALY

Converted to 2007 GBP using conversion factor of 0.585[10]

Analysis	Insulin	Absolute		Incremental		
		Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Analysis 1	NPH	40,026	11.034			
	Detemir	42,570	11.045	2,543	0.011	231,195
Analysis 2	NPH	39,441	11.097			
	Glargine	41,420	11.136	1,979	0.039	50,753

Sensitivity analyses

Deterministic: Sensitivity analysis showed that when fear of hypoglycaemia was accounted for ICERs decreased for both analysis, while when differences in HbA1c levels between insulins were ignored, ICERs increased significantly in both analysis. Other sensitivity analysis was published separately

Cameron et al (2009). Cost-effectiveness of insulin analogues for diabetes mellitus.[1]	
	Probabilistic: Detemir and Glargine had a 29.2% and 42.5% probability of being cost-effective at a WTP of Can($) 50,000/ QALY
Comments	**Source of funding:** Health Canada **Limitations:** Minor limitations (table 29)

Abbreviations: BMI, body mass index; CADTH, Canadian Agency for Drugs and Technologies in Health; Can$, Canadian dollar; CVD, Cardiovascular disease; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 2: Dawoud et al (2017)[11]

Dawoud et al (2017). Basal Insulin Regimens for Adults with Type 1 Diabetes Mellitus: A Cost-Utility Analysis.	
Study details	**Analysis** Cost utility analysis **Approach to analysis:** CORE Diabetes model 8.5 – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Include severe hypoglycaemic events, CVD, renal complications, eye disease, foot ulcer, neuropathy, and depression **Perspective:** UK National Health Service **Time horizon:** Lifetime **Discounting:** 3.5%
Interventions	**Intervention 1:** Detemir one daily **Intervention 2:** Detemir twice daily **Intervention 3:** Glargine 100 IU once daily **Intervention 4:** Degludec once daily **Intervention 5:** NPH once daily **Intervention 6:** NPH twice daily **Intervention 7:** NPH four times daily *Injection frequency: stated above; Insulin dose: average daily dose of 24 units daily was assumed for all comparators.*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** Mean age: 42.98; Male: 56.7%; Duration of diabetes (years): 16.92; BMI (kg/m2): 27.09; HbA1c (% points): 8.6; Weight (kg): NR
Data sources	**Resource use:** **Baseline/natural history:** Default CORE model values used unless information from UK based type1 diabetes population was available. This included CVD from health survey for England 2011, HbA1c levels, population characteristics and proportion of micro albuminuria from the national diabetes audit 2011-12, and cholesterol levels and proportion of neuropathy from Nathan et al[12]. **Effectiveness:** From network meta-analysis reported in NICE guideline 17, which was performed based on information gathered from a systematic review (25 studies reporting effectiveness for HbA1c levels, 11 studies for severe hypoglycaemic events).s **Costs:** Insulin costs were calculated using information from the British national formulary and MIMS June 2013. Needle cost were obtained from the average of the 10 most used needles. For costs from diabetes related complications, default CORE model costs were updated to reflect current UK costs. Sources for these include existing NICE guidelines, National Health Service reference costs, and major hypoglycaemic event costs from Hammer et al[13]. All costs were inflated to 2013 prices. **QoL:** Default QoL values in CORE model was used exception of disutility from severe hypoglycaemic events which were sourced from Currie et al[14]

Base-case results

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
NPH once daily	38,986	10.95			
NPH twice daily	39,585	10.97			ext. dom.
Glargine 100 IU once daily	40,007	11.04			ext. dom.
Detemir once daily	40,097	11.03			dominated
Detemir twice daily	40,404	11.09	397	0.05	7,940

Dawoud et al (2017). Basal Insulin Regimens for Adults with Type 1 Diabetes Mellitus: A Cost-Utility Analysis.						
	NPH four times daily	41,968	10.75			dominated
	Degludec once daily	43,096	10.99			dominated
Sensitivity analyses	**Deterministic:** Discount rate, hypoglycaemic event rates, disutility after hypoglycaemic event, cost of hypoglycaemic events, mortality risk after hypoglycaemic event, annual progressions of HbA1c levels, baseline cohort characteristics, insulin doses. **Scenario:** A "multiplicative approach" was used where the utility for patients with multiple complications was calculated as a multiplicative function of the utilities for these complications, compared to the base case which used the minimum utility value of all complications. **Results remained robust** to changes in input parameters and scenarios. **Probabilistic:** At a WTP of £20,000/QALY, Detemir (twice daily) had the highest probability of being cost-effective (26%). This increased to 41% at a WTP of £30,000.					
Comments	**Source of funding:** National Institute for Health and Care Excellence **Limitations:** Minor limitations (table 29)					

Abbreviations: BMI, body mass index; CVD, Cardiovascular disease; eq-5d, Euro-qol five dimensions, HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; MIMS, Monthly Index of Medical Specialities; NICE, National Institute for Health and Care Excellence; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 3: Ericcson et al (2012)[15]

Ericcson et al (2013). Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden.	
Study details	**Analysis:** Cost utility analysis **Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with hypoglycaemic events within a 1-year time horizon **Diabetes related complications considered:** Severe, non-severe daytime and non-severe nocturnal hypoglycaemic events **Perspective:** Swedish healthcare perspective **Time horizon:** 1 year **Discounting:** n/a
Interventions	**Intervention 1:** Degludec (dose ratio: 0.87) **Intervention 2:** Glargine (basal dose: 33.1 IU) *Injection frequency: not reported but assumed as once daily based on sensitivity analysis*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** NR
Data sources	**Resource use:** Insulin dose was obtained by conducting a meta-analysis. Assumed that all type1 diabetes patients carried out 28 SMGB test per week. **Baseline/natural history:** Rates of hypoglycaemic events from Swedish patients enrolled in multinational study[16] **Effectiveness:** From meta-analysis of trial comparing Degludec vs Glargine **Costs:** Insulin prices were obtained from pharmacy selling prices in Oct 2012, needle/ test strip/ lancet from TLV website in Dec 2012. Severe hypoglycaemic event costs from a costing study conducted in Sweden[17], and non-severe hypoglycaemic costs from resource use reported by Geelhoed-Duijvestijn et al[18]. All costs were inflated to 2012 prices **QoL:** Disutility from hypoglycaemic events from Swedish respondents in a multinational survey[19], QoL impact from SMGB tests from Diabetes Glycaemic Education and Monitoring study[20], and impact on QoL from flexible dosing from a time trade off study[19].

Base-case results

	Absolute		Incremental		
	Costs (SEK)	**QALYs**	**Costs (SEK)**	**QALYs**	**ICER**
Glargine	17,530	0.261			
Degludec	18,408	0.306	878	0.044	SEK19,766 /QALY

Converted to 2012 GBP using conversion factor of 0.08[10]

	Absolute		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
Glargine	1,421	0.261			

Ericcson et al (2013). Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden.						
	Degludec	1,492	0.306	71	0.044	1,618
Sensitivity analyses	**Deterministic:** Insulin dose, event rates of hypoglycaemic events, costs of hypoglycaemic events, mortality risks associated with hypoglycaemic events, number of SMGB tests used, impact of SMGB test on QoL, treatment effect of degludec vs glargine for hypoglycaemic events, injection frequency **Scenario:** cost-effectiveness of degludec compared to NPH **Results were most sensitive to** changes in treatment effect of degludec vs glargine for hypoglycaemic events. The scenario of degludec vs NPH resulted in an ICER of SEK 22,736/ QALY **Probabilistic:** Degludec had a 91.2% probability of being cost-effective at a threshold of SEK 500,000/QALY					
Comments	**Source of funding:** Novo Nordisk Scandinavia AB **Limitations:** Minor limitations (table 29)					

Abbreviations: BMI, body mass index; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SEK, Swedish Krona; SMGB, self-measured blood measured; WTP, willingness to pay

Table 4: Evans et al (2015)[21]

Evans et al (2015). Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with type 1 diabetes mellitus in the UK.						
Study details	**Analysis** Cost utility analysis **Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** Severe, non-severe daytime and non-severe nocturnal hypoglycaemic events **Perspective:** UK National Health Service **Time horizon:** 1 year **Discounting:** n/a					
Interventions	**Intervention 1:** Degludec (dose ratio: 0.87) **Intervention 2:** Glargine (basal: 33.1 IU) *Injection frequency: once daily*					
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** Mean age: N; Male: NR; Duration of diabetes (years): NR; BMI (kg/m2): <35; HbA1c (% points): <10; Weight (kg): NR					
Data sources	**Resource use:** Insulin dosage obtained from two phase three clinical trials[22,23] combined with a meta-analysis[24] to obtain dose ratios, needle use based on recommendations from the forum for injection technique for the UK. 28 SMGB tests per week assumed. **Baseline/natural history:** Two phase three clinical trials[22,23] **Effectiveness:** Form meta-analysis[24] **Costs:** Cost of Insulin, needles, test trips, etc sourced from MIMS (2013). Cost of hypoglycaemic events derived by using proportion of patients contacting hospitals after event was based on questionnaires in trial. This was combined with Cost derived from HRG tariffs, unit costs for social and health care 2011 & ISD Scotland. The year costs were inflated to was not reported. **QoL:** Disutility from hypoglycaemic events sourced from Evans et al[19]					
Base-case results		**Absolute**		**Incremental**		
		Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
	Glargine	2,112	NR			
	Degludec	2,250	NR	138	0.0082	16.895
Sensitivity analyses	**Deterministic:** Disutility after hypoglycaemic event, event rates of hypoglycaemic events, costs of hypoglycaemic events, rate of SMGB testing, dosage **Scenario:** Accounting for changes in utility given the availability of flexible dosing, using extended trial follow-up data. **Results were sensitive to** hypoglycaemic events rates, rate of SMGB testing, and insulin doses. **Probabilistic:** Degludec had probabilities of 55.98% & 67.89% of being cost-effective at a WTP thresholds of £20,000 & £30,000/ QALY					
Comments	**Source of funding:** Novo Nordisk **Limitations:** Minor limitations (table 29)					

Abbreviations: BMI, body mass index; eq-5d, Euro-qol five dimensions, HbA1c, glycosylated haemoglobin; HRG, Health resource group; ICER, incremental cost-effectiveness ratio; IU, international units; MIMS, Monthly Index of Medical Specialities; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 5: Evans et al (2015)[25]

Evans et al (2015). Insulin degludec early clinical experience: does the promise from the clinical trials translate into clinical practice--a case-based evaluation.	
Study details	**Analysis:** Cost utility analysis (effectiveness results not reported for base case) **Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Hypoglycaemic events included. Other complications unclear. **Perspective:** UK National Health Service **Time horizon:** Lifetime **Discounting: 3.5%**
Interventions	**Intervention 1:** Degludec **Intervention 2:** Detemir/ Glargine *Mean insulin dose of 7.1 units; Injection frequency: NR; Proportion of patients on Detemir/ Glargine: NR*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** Mean age: 35; Male: 42.9%; Duration of diabetes (years): 18.2; BMI (kg/m2): NR; HbA1c (% points): 9.4; Weight (kg): 77
Data sources	**Resource use:** Insulin use sourced from a single centre case series analysis of 35 type1 diabetes patients **Baseline/natural history:** Sourced from a single centre case series analysis of 35 type1 diabetes patients. **Effectiveness:** Sourced from a single centre case series analysis of 35 type1 diabetes patients **Costs:** NR **QoL:** NR

Base-case results

	Absolute		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
Glargine/ Detemir	822	NR			
Degludec	1,149	NR	327	NR	Dominant

Sensitivity analyses	**Deterministic:** Treatment effect of degludec vs glargine/detemir for HbA1c levels and hypoglycaemic events which had an impact on incremental QALYs **Probabilistic:** NR
Comments	**Source of funding:** Novo Nordisk **Limitations:** Very serious limitations (table 29)

Abbreviations: BMI, body mass index; eq-5d, Euro-qol five dimensions, HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; NR, not reported; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 6: Evans et al (2017)[26]

Evans et al (2017). Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Adults with Type 1 and Type 2 Diabetes Mellitus.	
Study details	**Analysis** Cost utility analysis **Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** Severe and non-severe hypoglycaemic events **Perspective:** UK National Health Service **Time horizon:** 1 year **Discounting:** n/a
Interventions	**Intervention 1:** Degludec (Dose ratio: 0.87) **Intervention 2:** Glargine U100 (Basal: 33.1 IU/day) *Injection frequency: once daily for both arms*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** NR
Data sources	**Resource use:** Insulin dosage derived from the Degludec clinical trial program, and information from a meta-analysis[24] to determine dose ratio. Needle use based on recommendations from the forum for injection technique for the UK. **Baseline/natural history:** Hypoglycaemic event rates from UKHSG study[27] **Effectiveness:** From two meta analyses[24,28]

Evans et al (2017). Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Adults with Type 1 and Type 2 Diabetes Mellitus.	
	Costs: Insulin costs from MIMS 2016. Needle costs from 2015 prescription cost analysis. Cost of severe hypoglycaemic events from study based in Germany, Spain and the UK[13] and non-severe hypoglycaemic events from study based in 11 countries including the UK[29]. Hypoglycaemic costs were inflated to 2015 prices. **QoL:** Disutility from hypoglycaemic events derived from large scale time trade-off study[19]

Base-case results

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Glargine U100	1,371.65	NR			
Degludec	1,330.42	NR	-41.23	0.0044	Dominant

Sensitivity analyses	**Deterministic: D**isutility after hypoglycaemic event, treatment effects of Detemir vs NPH for hypoglycaemic events, hypoglycaemic event rates, cost of hypoglycaemic events, injection frequency, insulin dose, insulin price. **Scenario:** Degludec vs Glargine biosimilar (Abasaglar), Degludec vs Glargine U300 **Results remained robust** to changes in input parameters. The scenario of Degludec vs Abasaglar resulted in an ICER £2,027/ QALY and the scenario of using Glargine U300 resulted in Degludec being dominant. In both these scenarios, only the price of insulins were changed. **Probabilistic:** Degludec had a 65% - 70% probability of being cost-effective at a WTP in excess of £10,000/ QALY
Comments	**Source of funding:** Novo Nordisk **Limitations:** Minor limitations (table 29)

Abbreviations: ICER, incremental cost-effectiveness ratio; IU, international units; MIMS, Monthly Index of Medical Specialities; n/a, not applicable; NPH, neutral protamine Hagedorn NR, not reported; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; UKHSG, UK Hypoglycaemia Study Group; WTP, willingness to pay

Table 7: Evans et al (2018)[30]

Evans et al (2018). Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting.	
Study details	**Analysis** Cost utility analysis **Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** Severe, non-severe nocturnal and non-severe daytime hypoglycaemic events **Perspective:** UK National Health Service **Time horizon:** 1 year **Discounting:** n/a
Interventions	**Intervention 1:** Degludec (Dose ratio: 0.97) **Intervention 2:** Glargine U100 (Basal: 31.93 IU/day) *Injection frequency: once daily for both arms*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** NR
Data sources	**Resource use:** Insulin use from SWITCH 1 trial[31]. Number of needles and SMGB tests were assumed to be the same in both arms. **Baseline/natural history:** Hypoglycaemic events from SWITCH 1[31] **Effectiveness:** From analysis of SWITCH 1 trial[31] using a Poisson model. **Costs:** Cost of insulin from MIMS 2018. Cost of severe hypoglycaemia from study based in Germany, Spain and the UK[13], non-severe hypoglycaemic events from Hypoglycaemia in insulin treated patients study[29]. Year to which prices were inflated to was not reported. **QoL:** Disutility after hypoglycaemic events from large scale time trade-off study[19]

Base-case results

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Glargine U100	1,505	0.7509			
Degludec	1,527	0.7741	22	0.0232	984

Sensitivity analyses	**Deterministic: D**isutility after hypoglycaemic event, treatment effects of Degludec vs Glargine U100 for hypoglycaemic events, hypoglycaemic event rates, costs of hypoglycaemic events, needles used per day, SMGB tests used, costs associated with loss in work productivity. **Scenario:** Accounting for changes in QoL due to availability of flexible dosing.

Evans et al (2018). Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting.	
	Results most sensitive to changes in hypoglycaemic event rates. **Probabilistic:** Degludec had a 99.8% probability of being cost-effective at a WTP of £20,000/ QALY
Comments	**Source of funding:** Novo Nordisk, Soborg, Denmark **Limitations:** Potentially serious limitations (table 29)

Abbreviations: ICER, incremental cost-effectiveness ratio; IU, international units; MIMS, Monthly Index of Medical Specialities; n/a, not applicable; NR, not reported; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 8: Grima et al (2007)[32]

Grima et al (2007). Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada.

Study details

Analysis: Cost utility analysis

Approach to analysis: CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables.

Diabetes related complications considered: Include hypoglycaemic events, CVD, retinopathy, nephropathy, and ketoacidosis

Perspective: Canadian public payer (ministry of health)

Time horizon: 36 years or until death

Discounting: 5%

Interventions

Intervention 1: Glargine (daily dose:22.26 IU)

Intervention 2: NPH (dose:27.17 IU)

Injection frequency: NR

Population

Population: Adults with Type 1 Diabetes

Characteristics: Mean age: 27; Male: NR; Duration of diabetes (years): NR; BMI (kg/m2): NR; HbA1c (% points): >7%; Weight (kg): NR

Data sources

Resource use: Insulin dosage sourced from Porcellati et al[33]

Baseline/natural history: Micro and macro vascular rates were derived from cumulative incidence over time graphs as reported in Palmer et al[2]. Event rates of other events based on published literature (source unclear). Baseline HbA1c levels were also sourced from Palmer et al[2]. The proportional change in complication risks with change in HbA1c levels were taken from type 2 patients in UKPDS 35[34]

Effectiveness: Sourced from Porcellati et al[33] who analyzed 121 type1 diabetes patients.

Costs: Insulin prices sourced from Canadian pharmaceutical price sources. Diabetes related complication costs sourced from 2 Canadian studies[35,36]. All costs adjusted to 2005 prices.

QoL: Utility values were sourced from Coffey et al[37] and a UKPDS publication[38]

Base-case results

	Absolute		Incremental		
	Costs (Can$)	**QALYs**	**Costs (Can$)**	**QALYs**	**ICER**
NPH	50,536	10.733			
Glargine	51,934	10.666	1,398	0.067	Can$ 20,799/ QALY

Converted to 2005 GBP using conversion factor of 0.58[10]

	Absolute		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
NPH	29,465	10.733			
Glargine	30,280	10.666	815	0.067	12,166

Sensitivity analyses

Deterministic: Model input parameters evaluated include treatment effects of Glargine vs NPH on HbA1c levels, baseline HbA1c levels, treatment costs of acute complications, discount rates, and utility values.

Results were most sensitive to treatment effects of Glargine vs NPH on HbA1c levels and baseline HbA1c levels.

Probabilistic: NR

Comments

Source of funding: Sanofi Aventis Canada

Limitations: Very serious limitations (table 29)

Abbreviations: BMI, body mass index; CVD, Cardiovascular disease; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral

protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; UKPDS, UK Prospective Diabetes Study; WTP, willingness to pay

Table 9: Gschwend et al (2009)[39]

Gschwend et al (2009). Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries.

Study details

Analysis: Cost utility analysis

Approach to analysis: CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables.

Diabetes related complications considered: Includes severe hypoglycaemic events, CVD, renal disease, amputation, vision impairment.

Perspective: Third party payer perspective in Belgium, France, Germany, Italy and Spain

Time horizon: 50 years

Discounting: 3% - 6% (country specific)

Interventions

Intervention 1: Detemir (dose: NR)

Intervention 2: NPH (dose: NR)

Injection frequency: NR

Population

Population: Adults with Type 1 Diabetes

Characteristics: Mean age: 35; Male: 54.7%; Duration of diabetes (years): 13; BMI (kg/m2): 24.7; HbA1c (% points): 8.3%, Weight (kg): NR

Data sources

Resource use: Insulin use based on end of trial doses (unclear as to what the trial was)

Baseline/natural history: Country specific simulation cohorts generated based on patient characteristics from the Bartley trial[40]. Pre-existing complication rates were obtained from a range of country specific sources.

Effectiveness: Unclear

Costs: Insulin, needle and SMGB test costs obtained from public pharmacies in specific countries. Direct medical costs were derived from a range of country specific sources. Cost were inflated to 2006 prices.

QoL: Derived from diabetes populations where possible[14,41–43]

Base-case results

Country	Insulin	Absolute		Incremental		
		Costs (€)	QALYs	Costs (€)	QALYs	ICER
Belgium	NPH	134,679	7.33			
	Detemir	122,737	7.85	–11,943	0.52	Dominant
France	NPH	63,321	7.92			
	Detemir	63,605	8.47	284	0.55	€519/ QALY
Germany	NPH	75,734	6.59			
	Detemir	74,880	7.04	–854	0.45	Dominant
Italy	NPH	90,139	8.39			
	Detemir	92,036	8.98	1,897	0.58	€3,256/ QALY
Spain	NPH	44,661	6.19			
	Detemir	44,085	6.59	-577	0.4	Dominant

Converted to 2006 GBP using conversion factors[10] of 0.80, 0.78, 0.82, 0.85, and 0.95 depending on the country

Country	Insulin	Absolute		Incremental		
		Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Belgium	NPH	107,292	7.33			
	Detemir	97,778	7.85	-9,514	0.52	Dominant
France	NPH	49,293	7.92			
	Detemir	49,515	8.47	221	0.55	402
Germany	NPH	62,234	6.59			
	Detemir	61,532	7.04	-702	0.45	Dominant
Italy	NPH	76,297	8.39			
	Detemir	77,903	8.98	1,606	0.58	2,768

Gschwend et al (2009). Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries.							
	Spain	**NPH**	42,263	6.19			
		Detemir	41,718	6.59	-545	0.4	Dominant
Sensitivity analyses	**Deterministic:** Model input parameters evaluated include discount rate, time horizon, treatment effects of Detemir vs NPH for HbA1c levels, severe hypoglycaemic events, BMI **Scenario:** Scenario considered where societal costs in terms of loss in productivity was included. **Results were most sensitive** to differences in major hypoglycaemic rates in the German context. Variations in time horizons also had a noticeable impact with smaller time horizons failing to capture long-term clinical outcomes and resulted in smaller benefits at lower costs. Same patterns were observed in France, Belgium, Italian and Spanish settings (data not shown) **Probabilistic:** Detemir had a 100% probability of being cost-effective at a WTP of €50,000 euros/ QALY in all 5 countries						
Comments	**Source of funding:** Novo Nordisk, Denmark **Limitations:** Very serious limitations (table 29)						

Abbreviations: BMI, body mass index; CVD, Cardiovascular disease; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 10: Haldrup et al (2020)[44]

Haldrup et al. (2020). Cost-effectiveness of switching to insulin degludec from other basal insulins in real-world clinical practice in Italy						
Study details	**Analysis** Cost utility analysis **Approach to analysis:** CORE Diabetes model 9.0 – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes hypoglycaemic events (severe, non-severe nocturnal, non-severe daytime), CVD, renal, retinopathy, macular edema, cataract, foot ulcer, neuropathy, and depression **Perspective:** Italian healthcare payer **Time horizon:** Lifetime **Discounting:** 3%					
Interventions	**Intervention 1:** Degludec (Dose ratio: 0.97) **Intervention 2:** Glargine U100 (73.8%)/ Detemir (23.9%)/ other basal insulin (2.3% (Basal dose: 20.64 IU/day) *Injection frequency: 49.9% of patients in EU-TREAT study were on once-daily regimens, and 45.8% on twice-daily at baseline*					
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** Mean age: 47.3; Male: 54.4%; Duration of diabetes (years): 21.2; BMI (kg/m2): 25; HbA1c (% points): 8.2; Weight (kg): NR					
Data sources	**Resource use:** Insulin use and dose ratios from EU-TREAT study (14). Dose ratios adjusted for covariates including number of daily injections. **Baseline/natural history:** Italian cohort of EU-TREAT (14) study to obtain baseline levels of hypoglycaemic events an HbA1c levels in other basal insulin am. Rates of other relevant complications were also obtained from Italian patients in EU-TREAT where available, with default CORE model values used otherwise **Effectiveness:** Italian cohort of EU-TREAT study to obtain treatment effects of Degludec vs other basal insulin for hypoglycaemic events and HbA1c levels. **Costs:** Insulin cost from Bella Republiblica Italiana Gazzetta 2017. Cost of needles and SMGB tests from public sources (25,26). Severe hypoglycaemic costs from HYPOS-1 study[45], non-severe hypoglycaemic costs from study on patient reported resource use, work-time loss and well-being costs from 7 European countries[18]. Other diabetic related complication costs sourced from a literature review and included public tariffs, government databases, registries publications, physicians' consortium publications, or health-economic technology appraisals. Cost were inflated to 2017 prices. **QoL:** Baseline utilities from a meta-analysis by Freemantle et al[46]. Disutility from hypoglycaemic events from eq-5d based time trade-off survey in 5 European countries[19]. Other QoL impact sources from a range of sources using eq-5d and other methods.					
Base-case results		**Absolute**		**Incremental**		
		Costs (€)	**QALYs**	**Costs (€)**	**QALYs**	**ICER**
	Others	201,672	9.544			
	Degludec	195,362	10.325	-6,310	0.781	Dominant

Haldrup et al. (2020). Cost-effectiveness of switching to insulin degludec from other basal insulins in real-world clinical practice in Italy	
	Converted to 2017 GBP using conversion factor of 0.993[10] **Absolute** / **Incremental** **Costs (£)** | **QALYs** | **Costs (£)** | **QALYs** | **ICER (£/QALY)** **Others**: 200,379 | 9.544 **Degludec**: 194,109 | 10.325 | -6,270 | 0.781 | Dominant
Sensitivity analyses	**Deterministic:** Model input parameters evaluated include discount rate, time horizon, disutility after hypoglycaemic event, treatment effects of Degludec vs other basal insulin for hypoglycaemic events and HbA1c levels. **Scenario:** Hypoglycaemic events as the only complication; Fresh needle and SMGB for every injection **Results most sensitive** to shorter time horizon and treatment effects for HbA1c levels **Probabilistic:** The NMB at a WTP of 30,000 euros of switching to degludec vs continuing previous basal insulin regimen was 29,710 euros
Comments	**Source of funding:** Novo Nordisk A/S **Limitations:** Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; eq-5d; CVD, Cardiovascular disease; Euro-qol five dimensions; EU-TREAT, EUropean TREsiba AUdit; GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 11: Hallin et al (2017)[47]

Hallin et al. (2017). Cost-effectiveness of switching to insulin degludec from other basal insulins: evidence from Swedish real-world data	
Study details	**Analysis** Cost utility analysis **Approach to analysis:** CORE Diabetes model 9.0 - a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal), CVD, renal, retinopathy, macular edema, cataract, foot ulcer, neuropathy, and depression **Perspective:** Swedish healthcare sector (direct healthcare costs financed by tax payments and co-payments) **Time horizon:** Lifetime **Discounting:** 3%
Interventions	**Intervention 1:** Degludec (Basal: 26.5 IU/day – rough estimate based on figure) **Intervention 2:** Glargine U100 (64%)/ Detemir (35%)/ NPH (1%) (Basal: 31 IU/day – rough estimate based on figure) *Injection frequency: once daily*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** Mean age: 46.29; Male: 56%; Duration of diabetes (years): 22.5; BMI (kg/m2): 26.1; HbA1c (% points): 8.39%; Weight (kg): NR
Data sources	**Resource use:** Insulin use from observational study conducted by DDC[48]. Sources of other resource use unclear. **Baseline/natural history:** Baseline characteristics including HbA1c levels were obtained from an observational study conducted by DDC[48]. Other complication rates were set at default levels except in the case of CVD complications[49,50], renal complications[51], retinopathy complications[50], and neuropathy[52] complications **Effectiveness:** Unclear but assumed to be from the observational study conducted by DDC[48] **Costs:** Cost of insulin, needles and SMGB tests assumed as pharmacy retail price. Default values in the CORE model used in cost of complications, except in the case of non-severe hypoglycaemic events (sourced from Geelhoed-Duijvestijn et al[18]) and severe hypoglycaemic events (sourced from Jonsson et al[52]. Cost were inflated to 2013 prices. **QoL:** Default values in the CORE model except in the case of non-severe hypoglycaemic events (sourced from Lauridsen et al[53]),severe hypoglycaemic events (sourced from Evans et al[19]) and utility of patients with no hypoglycaemic events (sourced from Freemantle et al[46])

Hallin et al. (2017). Cost-effectiveness of switching to insulin degludec from other basal insulins: evidence from Swedish real-world data

Base-case results

	Absolute		Incremental		
	Costs (SEK)	QALYs	Costs (SEK)	QALYs	ICER
Others	NR	NR			
Degludec	NR	NR	- 39,152	0.54	Dominant

Converted to 2013 GBP using conversion factor of 0.08[10]

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Others	NR	NR			
Degludec	NR	NR	-3,166	0.54	Dominant

Sensitivity analyses

Deterministic: Model input parameters evaluated include sensitivity analysis performed for treatment effects of Degludec vs Other basal insulin for HbA1c levels and hypoglycaemic events, duration of treatment effects, HbA1c progression, disutility from hypoglycaemic events, insulin prices, and insulin doses.

Scenario: Using alternate risk equations from UKPDS model and Pittsburg et al (reference not provided)

Results remained robust to changes in input parameters considered.

Probabilistic: NR

Comments

Source of funding: Novo Nordisk

Limitations: Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; eq-5d, CVD, Cardiovascular disease; DDC, Danderyd Diabetes Clinic; Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; QALYs, quality-adjusted life years; QoL, quality of life; SEK, Swedish Krona; SMGB, self-measured blood measured; UKPDS, UK Prospective Diabetes Study WTP, willingness to pay

Table 12: Lalic et al (2018)[54]

Lalic et al (2018). Cost-Effectiveness of Insulin Degludec Versus Insulin Glargine U100 in Patients with Type 1 and Type 2 Diabetes Mellitus in Serbia.

Study details

Analysis Cost utility analysis

Approach to analysis: Excel based model to calculate the direct cost and effectiveness (QALYs) associated with hypoglycaemic events within a 1-year time horizon.

Diabetes related complications considered: hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal)

Perspective: Serbian healthcare payer

Time horizon: 1 year

Discounting: n/a

Interventions

Intervention 1: Degludec (Dose ratio: 0.87)

Intervention 2: Glargine U100 (Basal: 33.1 IU/day)

Injection frequency: NR but assumed as once daily for both arms given the sensitivity analysis performed (of twice daily for Glargine U100)

Population

Population: Adults with Type 1 Diabetes

Characteristics: NR

Data sources

Resource use: end of trial doses from clinical data combined with dose ratios from a meta-analysis by Vora et al[24]

Baseline/natural history: Hypoglycaemic events rates of Degludec arm sourced from a largescale study in 7 European countries by Ostenson et al[16]

Effectiveness: Calculated by using information from 2 meta-analysis by Ratner et al[28] and Vora et al[24].

Costs: Direct treatment costs from RFZO 2017. Costs of hypoglycaemic events from Heller et al[55]. Direct treatment costs were inflated to 2017 prices

QoL: QoL impact from hypoglycaemic events sourced from time trade-off study based in 5 countries by Evans et al[19]

Base-case results

	Absolute		Incremental		
	Costs (RSD)	QALYs	Costs (RSD)	QALYs	ICER
Glargine U100	173,638	NR			
Degludec	185,628	NR	11,990	0.0287	RSD 417,586/QALY

Converted to 2017 GBP using conversion factor of 0.027[56]

Lalic et al (2018). Cost-Effectiveness of Insulin Degludec Versus Insulin Glargine U100 in Patients with Type 1 and Type 2 Diabetes Mellitus in Serbia.						
		Absolute		Incremental		
		Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
	Glargine U100	4,757	NR			
	Degludec	5,085	NR	328	0.0287	11,445
Sensitivity analyses	**Deterministic:** Model input parameters evaluated include time horizon, Costs of hypoglycaemic events, hypoglycaemic event rates, insulin dose, number of SMGB test per week, injection frequency. **Scenario:** Accounting for changes in QoL due to availability of flexible dosing. **Results most sensitive** to changes in hypoglycaemic event rates, insulin dose, and SMGB test used per week **Probabilistic:** Degludec had a 77.5% probability of being cost-effective at a WTP of RSD 2,048,112/ QALY					
Comments	**Source of funding:** Novo Nordisk **Limitations:** Minor limitations (table 29)					

Abbreviations: ICER, incremental cost-effectiveness ratio; GBP, Great British Pounds; IU, international units; n/a, not applicable; NR, not reported; QALYs, quality-adjusted life years, QoL, quality of life; RSD, Serbian dinar; SMGB, self-measured blood measured; WTP, willingness to pay

Table 13: McEwan et al (2007)[57]

McEwan et al (2007). Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK							
Study details	**Analysis:** Cost utility analysis **Approach to analysis:** Discrete event simulation model which uses transition functions for the development of five vascular and two glycaemic complications to simulate disease progression in type 1 diabetes patients. The model was based on a simplified version disease progression by Palmer et al[58]. **Diabetes related complications considered:** include CVDs, renal disease, amputation, vision loss, hypoglycaemic events (severe, nocturnal, and symptomatic), and ketoacidosis. **Perspective:** UK National Health Service **Time horizon:** 40 years **Discounting:** 3.5%						
Interventions	**Intervention 1:** Glargine (dose: NR) **Intervention 2:** NPH (dose: NR) *Injection frequency: NR*						
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** Mean age: 27; Male: 54%; Duration of diabetes (years): NR; BMI (kg/m2): NR; HbA1c (% points): 8.8; Weight (kg): 72						
Data sources	**Resource use:** NR **Baseline/natural history:** Baseline characteristics obtained from DCCT trial[59]. Other complications and disease progression developed from a range of original sources[58,60–63] **Effectiveness:** Form a meta-analysis conducted by Medical Research Matters Ltd for Sanofi-Aventis. **Costs:** Insulin costs obtained from British National Formulary. Cost of hypoglycaemic events sources from Leese et al[64]. Cost of vascular complication from[65], renal complications from UK drug tariffs and McEwan et al[66] and retinopathy from Palmer et al[58]. All cost inflated to 2005 prices. **QoL:** QoL estimates were derived from either the UKPDS[65] or HODaR database[67,68] and in the case of Hypoglycaemic events from Currie et al[14]. In all of these sources, QoL was measured using eq-5d.						
Base-case results	**Scenario**	**Insulin**	**Absolute**		**Incremental**		
			Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
	Scenario 1	**NPH**	8,708	10.84			
		Glargine	9,805.4	10.97	1,097.4	0.12	8,807.3
	Scenario 2	**NPH**	8,703.4	10.84			
		Glargine	9,783.5	10.97	1,080.1	0.12	8,667.9
	Scenario 3	**NPH**	8,703.4	10.84			
		Glargine	9,746.6	10.99	1,043.2	0.14	7,391.1
	Scenario 4	**NPH**	8,712.97	10.85			
		Glargine	10,084.17	10.99	1,371.2	0.14	9,767.46
	Scenario 5	**NPH**	8,825.09	10.83			

McEwan et al (2007). Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK							
		Glargine	9,921.36	11.18	1,096.27	0.34	3,189.44
Sensitivity analyses	**Deterministic:** Model input parameters evaluated include age of population, price of Glargine, Cost of hypoglycaemic events, hypoglycaemic event rates, disutility from hypoglycaemic events, weight of patients. **Scenario:** Various scenarios were conducted where different inputs for treatment effects of Glargine vs NPH for hypoglycaemic events and HbA1c levels was assumed. **Results were most sensitive to** price of glargine, disutility post hypoglycaemic events, and the cohorts' mean weight **Probabilistic:** NR						
Comments	**Source of funding:** Sanofi Aventis **Limitations:** Very serious limitations (table 29)						

Abbreviations: BMI, body mass index; CVD, Cardiovascular disease; DCCT, Diabetes Control and Complications Trial;eq-5d, Euro-qol five; GBP, Great British Pounds; NPH, neutral protamine Hagedorn dimensions, HbA1c, glycosylated haemoglobin; HODaR, Health Outcomes Data Repository; ICER, incremental cost-effectiveness ratio; IU, international units;; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 14: Mezquita-Raya et al (2017)[69]

Mezquita-Raya et al (2017). Cost-effectiveness analysis of insulin degludec compared with insulin glargine u100 for the management of type 1 and type 2 diabetes mellitus - from the Spanish National Health System perspective.

Study details	**Analysis** Cost utility analysis **Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** hypoglycaemic events (severe, non-severe) **Perspective:** Spanish national health service **Time horizon:** 1 year **Discounting:** n/a
Interventions	**Intervention 1:** Degludec (Dose ratio: 0.87) **Intervention 2:** Glargine (Basal: 33.1 IU/day) *Injection frequency: once daily for both arms*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** NR
Data sources	**Resource use:** Insulin doses based on information from meta-analysis[24]. SMGB tests based on information from a previous economic evaluation by Evans et al[21]. Number of needles assumed to be equal for both regiments **Baseline/natural history:** Hypoglycaemic event rates based on information derived from Spanish observational study[70] **Effectiveness:** From meta-analysis of phase 3a trials[28] **Costs:** Insulin costs from Spanish medication database. Needle and SMGB costs from Spanish Ministry of Health. Cost of severe hypoglycaemic events from Hammer et al[13]. For non-severe hypoglycaemic events the cost of additional SMGB test were taken into account based on information from Brod et al[71]. All costs inflated to 2016 prices. **QoL:** Impact on Qol from hypoglycaemic events based on time trade-off study by Evans et al[19]

Base-case results

	Absolute		Incremental		
	Costs (€)	**QALYs**	**Costs (€)**	**QALYs**	**ICER**
Glargine	1,763.13	NR			
Degludec	1,764.24	NR	1.11	0.0211	52.7 €/QALY

Converted to 2016 GBP using conversion factor of 1.07[10]

	Absolute		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
Glargine	1,889	NR			
Degludec	1,890	NR	1.19	0.0211	56

Sensitivity analyses	**Deterministic:** Model input parameters evaluated include disutility after hypoglycaemic event, treatment effects of Degludec vs Glargine for hypoglycaemic events, insulin dose, injections per day, number of SMGB tests performed **Results most sensitive** to changes number of SMGB tests performed **Probabilistic:** Degludec had an 86.42% probability of being cost-effective at a WTP of €30,000/ QALY

Mezquita-Raya et al (2017). Cost-effectiveness analysis of insulin degludec compared with insulin glargine u100 for the management of type 1 and type 2 diabetes mellitus - from the Spanish National Health System perspective.	
Comments	**Source of funding:** Novo Nordisk Pharma SA **Limitations:** Minor limitations (table 29)

Abbreviations: GBP, Great British Pounds; ICER, incremental cost-effectiveness ratio; IU, international units; n/a, not applicable; NR, not reported; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 15: Morales et al (2015)[72]

Morales et al (2015). Cost-Effectiveness Analysis of Insulin Detemir Compared to Neutral Protamine Hagedorn (NPH) in Patients with Type 1 and Type 2 Diabetes Mellitus in Spain

Study details

Analysis Cost utility analysis
Approach to analysis: Excel based model to calculate the direct cost and effectiveness (QALYs) associated with non-severe hypoglycaemic events within a 1-year time horizon.
Diabetes related complications considered: non-severe hypoglycaemic events
Perspective: Spanish national health service
Time horizon: 1 year
Discounting: n/a

Interventions

Intervention 1: Detemir (daily dose of 40 IU)
Intervention 2: NPH (daily dose of 40 IU)
Injection frequency: not reported

Population

Population: Adults with Type 1 Diabetes
Characteristics: NR

Data sources

Resource use: Dosage of insulin obtained from recommendations from the World Health Organisation.
Baseline/natural history: Scenario1: UK Hypoglycaemia Study[27] patients receiving insulin < 5 years; scenario 2: UK Hypoglycaemia Study[27]patients receiving insulin > 15 years; scenario 3: Spanish cohort by Orozco et al[70]
Effectiveness: Meta-analysis by Canadian agency for Drugs and Technology[73]
Costs: Direct costs sourced from pharmacy prices as reimbursed by the Spanish NHS. Non-severe hypoglycaemic events consist of 5.6 glucose test strips. It was also assumed that 25% of the cohort visits a General Practitioner. Costs inflated to 2014 prices.
QoL: Sourced from previous economic evaluation by Evans et al[21]

Base-case results

		Absolute		Incremental		
		Costs (€)	QALYs	Costs (€)	QALYs	ICER
Scenario 1	NPH	382.78	0.843			
	Detemir	575.26	0.868	192.48	0.025	€7681.96 /QALY
Scenario 2	NPH	415.36	0.808			
	Detemir	602.69	0.839	187.25	0.031	€6,105.08 /QALY
Scenario 3	NPH	678.29	0.525			
	Detemir	823.49	0.601	145.20	0.076	€1909.70 /QALY

Converted to 2014 GBP using conversion factor of 1.05[10]

		Absolute		Incremental		
		Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Scenario 1	NPH	404	0.84			
	Detemir	607	0.87	203	0.03	8,119
Scenario 2	NPH	438	0.81			
	Detemir	636	0.84	197	0.03	6,369
Scenario 3	NPH	715	0.53			
	Detemir	868	0.60	153	0.08	2,015

Sensitivity analyses

Deterministic: Model input parameters evaluated include event rates for minor hypoglycaemic events, costs of minor hypoglycaemic events, disutility after hypoglycaemic event, cost of insulin therapies, treatment effects of Detemir vs NPH for hypoglycaemic events, weigh gain differences between detemir and NPH.

Morales et al (2015). Cost-Effectiveness Analysis of Insulin Detemir Compared to Neutral Protamine Hagedorn (NPH) in Patients with Type 1 and Type 2 Diabetes Mellitus in Spain	
	Results were most sensitive to changes in treatment effects of Detemir vs NPH for hypoglycaemic events and cost of detemir. **Probabilistic:** Detemir had a probability of 89.5% of being cost-effective at a WTP of €30,000 / QALY
Comments	**Source of funding:** Novo Nordisk **Limitations:** Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; eq-5d, Euro-qol five dimensions, HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; GBP, Great British Pounds; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; Scen, scenario; SMGB, self-measured blood measured; WTP, willingness to pay

Table 16: Palmer et al (2004)[74]

Palmer et al (2004). Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials.	
Study details	**Analysis:** Cost utility analysis **Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** include CVDs, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, and amputation **Perspective:** UK National Health Service **Time horizon:** Lifetime **Discounting:** 3.5%
Interventions	**Intervention 1:** Detemir (dose: NR) **Intervention 2:** NPH (dose: NR) *Injection frequency: NR*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics (Detemir/ NPH):** Mean age: 40.2/ 39.6; Male: 61.6%/ 60.6%; Duration of diabetes (years): NR; BMI (kg/m2): 25.1/ 25.2; HbA1c (% points): 8.36/ 8.36; Weight (kg): 75.4/ 75.3
Data sources	**Resource use:** NR **Baseline/natural history:** Combination of meta-analysis, UK specific data for type1 diabetes and trial population characteristics from Hermansen et al[75] **Effectiveness:** Meta-analysis of clinical trials comparing Detemir vs NPH **Costs:** Cost of insulin obtained from MIMS 2004. Cost of diabetes related complications obtained from the UKPDS[65,76] and a range of other sources[77–80] which reported diabetes specific costs (no reference costs were used). All costs were inflated to 2003 prices. **QoL:** Health state utilities were derived where possible from UKPDS[81], with gaps filled in using information from the Australian Institute of Health and Welfare burden of illness in Australia report[41], Tengs et al[43], and QoL decrements after major hypoglycaemic events from a NICE guidelines update in 2002[81]
Base-case results	

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
NPH	32, 698	NR			
Detemir	34,405	NR	1,707	0.09	19,285

Sensitivity analyses	**Deterministic:** Model input parameters evaluated include time horizon, Limiting treatment effects to only changes in HbA1c levels, discount rates, cost of major hypoglycaemic events. **Scenario:** Analysis performed using a cohort of newly diagnosed type 1 diabetes patients. **Results most sensitive** to changes in time horizon and when limiting treatment effects to changes in HbA1c levels. **Probabilistic:** Detemir had a 58% probability of being cost-effective at a WTP of £30,000/ QALY
Comments	**Source of funding:** Novo Nordisk A/S, Denmark **Limitations:** Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; eq-5d, CVD, Cardiovascular disease; Euro-qol five dimensions, HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; MIMS, Monthly Index of Medical Specialities; NICE, National Institute for Health and Care Excellence; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; UKPDS, UK Prospective Diabetes Study; WTP, willingness to pay

Table 17: Palmer et al (2007)[82]

Palmer et al (2007). An economic assessment of analogue basal-bolus insulin versus human basal-bolus insulin in subjects with type 1 diabetes in the UK.	
Study details	**Analysis:** Cost utility analysis **Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** include CVDs, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, and amputation **Perspective:** UK National Health Service **Time horizon:** Lifetime **Discounting:** 3.5%
Interventions	**Intervention 1:** Detemir (dose: NR) **Intervention 2:** NPH (dose: NR) *Injection frequency: NR*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** Mean age: 39.1; Male: 63.2%; Duration of diabetes (years): 15.3; BMI (kg/m2): 24.9; HbA1c (% points): 8.38%; Weight (kg): 73.8
Data sources	**Resource use:** End of clinical trial data as reported by Hermansen et al[75] **Baseline/natural history:** From trial data as reported by Hermansen et al[75]. In instances where required parameters were not reported in this study, inputs were sourced from other UK specific diabetes populations. **Effectiveness:** From trial data as reported by Hermansen et al[75] **Costs:** Insulin costs from MIMS 2004. Cost of diabetes specific complications from UK specific sources[79,80]. All costs inflated to 2004 prices **QoL:** Health state utilities mainly derived from UKPDS[75]. Disutility from major hypoglycaemic events were sourced from Currie et al[83] and minor from a NICE guideline update in 2002[81]
Base-case results	

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
NPH	NR	NR			
Detemir	NR	NR	1,654	0.66	2,500

Sensitivity analyses	**Deterministic:** Model input parameters evaluated include time horizon, Limiting treatment effects to only changes in HbA1c levels, discount rates, cost of major hypoglycaemic events. **Results most sensitive** to when limiting treatment effects to changes in HbA1c levels. **Probabilistic:** Detemir had a 95% probability of being cost-effective at a WTP of £25,000/ QALY
Comments	**Source of funding:** Novo Nordisk A/S, Bagsvaerd, Denmark **Limitations:** Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; CVD, Cardiovascular disease; eq-5d, Euro-qol five dimensions, HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; MIMS, Monthly Index of Medical Specialities; NICE, National Institute for Health and Care Excellence; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; UKPDS, UK Prospective Diabetes Study; WTP, willingness to pay

Table 18: Pedersen-Bjergaard et al (2016)[84]

Pedersen-Bjergaard et al (2016). Short-term cost-effectiveness of insulin detemir and insulin aspart in people with type 1 diabetes who are prone to recurrent severe hypoglycaemia.	
Study details	**Analysis** Cost utility analysis **Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal) **Perspective:** Danish healthcare payer perspective **Time horizon:** 1 year **Discounting:** n/a
Interventions	**Intervention 1:** Detemir (basal daytime: 23.9 IU; basal bedtime: 17.3) **Intervention 2:** NPH (basal daytime: 20.2 IU; basal bedtime: 16.3) *Injection frequency: not reported – Hypo Ana study did not specify frequency*
Population	**Population:** Adults with Type 1 Diabetes

<table>
<tr><th colspan="2">Pedersen-Bjergaard et al (2016). Short-term cost-effectiveness of insulin detemir and insulin aspart in people with type 1 diabetes who are prone to recurrent severe hypoglycaemia.</th></tr>
<tr><td></td><td>Characteristics: Mean age: 54; Male: 56%; Duration of diabetes (years): 30; BMI (kg/m2): 24.8; HbA1c (% points): 8; Weight (kg):NR</td></tr>
<tr><td>Data sources</td><td>Resource use: Insulin dosage sourced from end of trial data.
Baseline/natural history: From the HypoAna study population[85–87]
Effectiveness: From the HypoAna study population[85–87]
Costs: Insulin prices from Danish health and medicine authority. SMGB test and needle prices from prices published by Nomeco. Sever hypoglycaemic event cost derived using information from doctor and emergency room visits, and pre-hospital treatments. Costs inflated to 2015 prices.
QoL: Baseline Qol and disutility from hypoglycaemic events from TTO by Evans et al[19]</td></tr>
<tr><td>Base-case results</td><td>
<table>
<tr><th></th><th colspan="2">Absolute</th><th colspan="3">Incremental</th></tr>
<tr><th></th><th>Costs (DKK)</th><th>QALYs</th><th>Costs (DKK)</th><th>QALYs</th><th>ICER</th></tr>
<tr><td>NPH</td><td>18,558</td><td>0.4502</td><td></td><td></td><td></td></tr>
<tr><td>Detemir</td><td>20,418</td><td>0.5174</td><td>1,860</td><td>0.0672</td><td>27,685 DKK /QALY</td></tr>
</table>
Converted to 2015 GBP using conversion factor of 0.095[10]
<table>
<tr><th></th><th colspan="2">Absolute</th><th colspan="3">Incremental</th></tr>
<tr><th></th><th>Costs (£)</th><th>QALYs</th><th>Costs (£)</th><th>QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>NPH</td><td>1,759</td><td>0.450</td><td></td><td></td><td></td></tr>
<tr><td>Detemir</td><td>1,936</td><td>0.517</td><td>176</td><td>0.067</td><td>2,624</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity analyses</td><td>Deterministic: Model input parameters evaluated include disutility after hypoglycaemic event, treatment effects of Detemir vs NPH for hypoglycaemic events
Results remained robust to changes in input parameters considered.
Probabilistic: NR</td></tr>
<tr><td>Comments</td><td>Source of funding: Novo Nordisk A/S
Limitations: Very serious limitations (table 29)</td></tr>
</table>

Abbreviations: BMI, body mass index; DKK, Denmark Krone; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 19: Pfohl et al (2012)[88]

<table>
<tr><th colspan="2">Pfohl et al (2012). Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany</th></tr>
<tr><td>Study details</td><td>Analysis Cost utility analysis
Approach to analysis: CRC DES model[57,89] – a MS Excel and C++ based model derived from the CORE model. It uses transition functions for the development of two acute (glycaemic) and five long-term (vascular) complications to simulate disease progression in T1D patients
Diabetes related complications considered: include first stroke, myocardial infarction, hypoglycaemic events (sever, non-severe daytime, non-severe nocturnal), ketoacidosis, end-stage renal disease, severe vision loss and amputation
Perspective: Statutory Health Insurance in Germany
Time horizon: 40 years
Discounting: 3%</td></tr>
<tr><td>Interventions</td><td>Intervention 1: Glargine (0.32 units per kg bodyweight per day)
Intervention 2: NPH (0.38 units per kg bodyweight per day)
Injection frequency: NR</td></tr>
<tr><td>Population</td><td>Population: Adults with Type 1 Diabetes
Characteristics: Mean age: 34.8; Male: 52.6%; Duration of diabetes (years): 13.4; BMI (kg/m2): NR; Weight (kg): 76.6; HbA1c (% points): 8.8%</td></tr>
<tr><td>Data sources</td><td>Resource use: Source unclear as reference is in German
Baseline/natural history: Baseline glycaemic events were based on information from DCCT[59]. Vascular events were predicted using UKPDS risk engine[90].
Effectiveness: Meta-regression analysis by Mullins et al[91]
Costs: Insulin, needle and test strip costs were calculated using German pricing source (accounting for discounts and co-payments patients are allowed. Cost of event related treatment costs were calculated using</td></tr>
</table>

Pfohl et al (2012). Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany	
	information from publications in a German setting[80,92] which included inpatient and outpatient costs, when default model values[91] were not used. Insulin costs were at 2010 prices, other costs at 2010 prices. **QoL:** Disutility after events were based on those provided by the CRC DES model[57,89] which was calculated using information from sources in the literature[14,93,94] using the eq-5d measurement tool.
Base-case results	

	Absolute		Incremental		
	Costs (€)	QALYs	Costs (€)	QALYs	ICER
NPH	30,890	10.92			
Glargine	25,644	11.31	-5,246	0.397	Dominant

Converted to 2010 GBP using conversion factor of 0.87[10]

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
NPH	26,946	10.92			
Glargine	22,369	11.31	-4,576	0.397	Dominant

Sensitivity analyses	**Deterministic:** Model input parameters evaluated include insulin costs, event related treatment costs, discount rates, hypoglycaemic rates, disutility from all adverse events, cardiovascular risks, treatment effects for hypoglycaemic events and HbA1c levels of Glargine vs NPH, time horizon **Scenario analysis:** Source characteristics and risk factors from German T1D patients (as far as available) **Results most sensitive to** changes in risk factors and treatment effects on HbA1c levels by Glargine vs NPH **Probabilistic:** Scatterplot shows that Glargine was dominant in 80.4% of iterations.
Comments	**Source of funding:** Sanofi-Aventis Deutschland GmbH **Limitations:** Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; CRC DES, Cardiff research consortium discrete event simulation model; DCCT, Diabetes Control and Complications Trial; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; UKPDS, UK Prospective Diabetes Study; WTP, willingness to pay

Table 20: Pollock et al (2017)[95]

Pollock et al (2017). A short-term cost-utility analysis of insulin degludec versus insulin glargine U100 in patients with type 1 or type 2 diabetes in Denmark.	
Study details	**Analysis** Cost utility analysis **Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal) **Perspective:** Danish healthcare payer perspective **Time horizon:** 1 year **Discounting:** n/a
Interventions	**Intervention 1:** Degludec (Dose ratio: 0.87) **Intervention 2:** Glargine U100 (Basal: 33.1 IU/day) *Injection frequency: once daily for both arms*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** NR
Data sources	**Resource use:** Insulin dosage from BEGIN trial program[24] **Baseline/natural history:** Hypoglycaemic rates sourced from Danish patients in Ostenson et al[16] **Effectiveness:** From a meta-analysis of trials in the BEGIN trial program[24] **Costs:** Cost of severe hypoglycaemic events sourced from HypoAnna study in a previous economic evaluation[84]. Non-sever hypoglycaemic event costs assumed to be 2.1 times SMGB test costs and general practitioner costs. Costs inflated to 2016 prices. **QoL:** Disutility associated with hypoglycaemic events sourced from Evans et al[19]
Base-case results	

	Absolute		Incremental		
	Costs (DKK)	QALYs	Costs (DKK)	QALYs	ICER
Glargine U100	24,712	0.7841			
Degludec	23,219	0.7877	-1,493	0.0036	Dominant

Pollock et al (2017). A short-term cost-utility analysis of insulin degludec versus insulin glargine U100 in patients with type 1 or type 2 diabetes in Denmark.	
	Converted to 2016 GBP using conversion factor of 0.097[10]

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Glargine U100	2,404	0.7841			
Degludec	2,258	0.7877	-145	0.0036	Dominant

Sensitivity analyses	**Deterministic:** Model input parameters evaluated include insulin dose, treatment effects of Degludec vs Glargine U100 for hypoglycaemic events, mortality after severe hypoglycaemic event **Scenario:** Comparing Degludec vs Biosimilar Glargine U100 (Absaglar) by changing prices of Glargine U100 to those of Abasaglar. **Results remained robust** to different scenarios and changes in input parameters. Scenario analysis comparing Degludec to Abasaglar resulted in an ICER of DKK 62,945 (£6,122) / QALY for Degludec **Probabilistic:** Degludec had an 83.3% probability of being cost-effective at a WTP of DKK 250,000/ QALY
Comments	**Source of funding:** Novo Nordisk Healthcare AG **Limitations:** Minor limitations (table 29)

Abbreviations: DKK, Denmark Krone; GBP, Great British Pounds; ICER, incremental cost-effectiveness ratio; IU, international units; n/a, not applicable; NR, not reported; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 21: Pollock et al (2018)[96]

Pollock et al (2018). Evaluating the cost-effectiveness of insulin detemir versus neutral protamine hagedorn insulin in patients with type 1 or type 2 diabetes in the UK using a short-term modelling approach.	
Study details	**Analysis** Cost utility analysis **Approach to analysis:** Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon. **Diabetes related complications considered:** non-severe hypoglycaemic events **Perspective:** UK National Health Service **Time horizon:** 1 year **Discounting:** n/a
Interventions	**Intervention 1:** Detemir (Dose ratio: 1) **Intervention 2:** NPH (Basal: 24.35 IU/day) *Injection frequency: NR*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** NR
Data sources	**Resource use:** Sourced from the DAFNE program[97]. SMGB tests performed accounted for in accordance with NICE guidelines. **Baseline/natural history:** Hypoglycaemic rates obtained from UK specific study[98] **Effectiveness:** From a meta-analysis performed by the Canadian Agency for Drugs and Technology in Health[73] **Costs:** Insulin costs sourced from the British National Formulary. Cost of needles and SMGB tests from the NHS Business service authority. Cost of non-severe hypoglycaemic events sourced from an analysis of 10 countries in the UK[29]. Cost inflated to 2016 prices. **QoL:** Disutility from non-severe hypoglycaemic events sourced from Evans et al[19]

Base-case results

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
NPH	1,241	0.192			
Detemir	1,301	0.291	60	0.099	610

Sensitivity analyses	**Deterministic:** Model input parameters evaluated include disutility after hypoglycaemic event, treatment effects of Detemir vs NPH for hypoglycaemic events, hypoglycaemic event rates **Scenario:** Assuming a diminishing marginal utility approach. **Results most sensitive** to changes in hypoglycaemic event rates **Probabilistic:** Detemir had a 99.9% probability of being cost-effective at a WTP of £10,000/ QALY
Comments	**Source of funding:** Novo Nordisk Limited **Limitations:** Potentially serious limitations (table 29)

Abbreviations: DAFNE, Dose Adjustment For Normal Eating; ICER, incremental cost-effectiveness ratio; IU, international units; n/a, not applicable; NICE, National Institute for Health and Care Excellence; NPH, neutral protamine Hagedorn; NR, not reported; QALYs, quality-adjusted life years; QoL, quality of life; WTP, willingness to pay

Table 42: Russel-Szymczyk et al (2019)[99]

Russel-Szymczyk et al (2019). Cost-effectiveness of insulin degludec versus insulin glargine U100 in adults with type 1 and type 2 diabetes mellitus in Bulgaria.

Study details

Analysis Cost utility analysis
Approach to analysis: Excel based model to calculate the direct cost and effectiveness (QALYs) associated with minor hypoglycaemic events within a 1-year time horizon.
Diabetes related complications considered: hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal)
Perspective: Bulgarian national insurance fund
Time horizon: 1 year
Discounting: n/a

Interventions

Intervention 1: Degludec (Dose ratio: 0.87)
Intervention 2: Biosimilar Glargine U100 (Basal: 28.11 IU/day)
Injection frequency: 49.9% of patients in EU-TREAT study were on once-daily regimens, and 45.8% on twice-daily at baseline

Population

Population: Adults with Type 1 Diabetes
Characteristics: NR

Data sources

Resource use: Insulin dosage in from clinical practise in Bulgaria[100]
Baseline/natural history: Non-severe hypoglycaemic event rates sourced from UKHSG[27,101]
Effectiveness: From a meta-analysis by Ratner et al(27)
Costs: Cost of insulin based on pharmacy selling prices. Cost of needles and SNGB tests not reimbursed and hence directly by patients. Cost of hypoglycaemic events sourced from a previous analysis[54]. Cost inflated to 2018 prices.
QoL: Disutility from hypoglycaemic events sourced from a previous analysis[54]

Base-case results

	Absolute		Incremental		
	Costs (BGN)	QALYs	Costs (BGN)	QALYs	ICER
Biosimilar Glargine U100	3,073.92	0.5568			
Degludec	3,143.28	0.5722	69.37	0.0154	BGN4,498/ QALY

Converted to 2018 GBP using conversion factor of 1.75[56]

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Biosimilar Glargine U100	1,241	0.192			
Degludec	1,301	0.291	60	0.099	606

Sensitivity analyses

Deterministic: Model input parameters evaluated include time horizon, cost of hypoglycaemic event, mortality after hypoglycaemic event, hypoglycaemic event rates, insulin dose ratio
Scenario:
Results most sensitive to changes in hypoglycaemic event rates
Probabilistic: At a threshold of 39,619 BGN/QALY Degludec had a 60% probability of being cost effective.

Comments

Source of funding: Novo Nordisk A/S
Limitations: Potentially serious limitations (table 29)

Abbreviations: BGN, Bulgarian Lev; EU-TREAT, EUropean TREsiba AudiT; GBP, Great British Pounds; ICER, incremental cost-effectiveness ratio; IU, international units; n/a, not applicable; NR, not reported; QALYs, quality-adjusted life years; QoL, quality of life; UKHSG, UK Hypoglycaemia Study Group; WTP, willingness to pay

Table 23: Tunis et al (2009)[102]

Tunis et al (2009). Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis.

Study details

Analysis: Cost utility analysis

Tunis et al (2009). Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis.	
	Approach to analysis: CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes severe hypoglycaemic events (severe and non-severe), CVD, renal disease, amputation, vision impairment, foot ulcer, and peripheral neuropathy. **Perspective:** Canadian provincial government **Time horizon:** 60 years **Discounting:** 5%
Interventions	**Intervention 1:** Detemir (dose: NR) **Intervention 2:** NPH (dose: NR) *Injection frequency: NR*
Population	**Population:** Adults with Type 1 Diabetes **Characteristics:** Mean age: 27; Male: 54%; Duration of diabetes (years): 9; BMI (kg/m2): 23.75; HbA1c (% points): 8.9; Weight: NR
Data sources	**Resource use:** NR **Baseline/natural history:** Obtained from the DCCT secondary intervention cohort[10359] and the visible minority population report (2005) by Statistics Canada. **Effectiveness:** From a single trial conducted by Bartley et al[40] **Costs:** Drug prices obtained from Nov Scotia pharmacy selling prices. Cost of complications taken from publicly available online sources[7,8,35,366,104].Cost inflated to 2007 prices. **QoL:** Disutility from hypoglycaemic events sourced from Currie et al[14]. Other health utilities were obtained from another study looking at the cost-effectiveness of insulin analogues for diabetes patients[105]
Base-case results	

	Absolute		Incremental		
	Costs (Can$)	**QALYs**	**Costs (Can$)**	**QALYs**	**ICER**
NPH	72,016	9.354			
Detemir	83,622	9.829	11,606	0.475	Can$ 24,839/ QALY

Converted to 2007 GBP using conversion factor of 0.597[10]

	Absolute		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
NPH	42,161	9.354			
Detemir	48,955	9.829	6,795	0.475	14,304

Sensitivity analyses	**Deterministic:** Model input parameters evaluated include discount rates, disutility from hypoglycaemic events, **Results most sensitive to** disutility from hypoglycaemic events. **Probabilistic:** Detemir had a 46.2%, 56.1%, % 61.3% probability of being cost-effective at a WTP of Can($) 20,000, 30,000, & 40,000/ QALY respectively
Comments	**Source of funding:** Novo Nordisk **Limitations:** Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; Can$, Canadian dollar; eq-5d, CVD, Cardiovascular disease; DCCT, Diabetes Control and Complications Trial;Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 24: Valentine et al (2006)[106]

Valentine et al (2006). Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH.	
Study details	**Analysis:** Cost utility analysis **Approach to analysis:** CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables. **Diabetes related complications considered:** Includes severe hypoglycaemic events (severe and non-severe), CVDs, amputation, vision impairment, foot ulcer, and peripheral neuropathy. retinopathy, macular edema, vision loss, and cataract

Valentine et al (2006). Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH.

Perspective: US health care system
Time horizon: 35 years
Discounting: 3%

Interventions

Analysis 1:
Intervention 1: Detemir (dose: NR)
Intervention 2: NPH (dose: NR)
Injection frequency:
Analysis 2:
Intervention 1: Glargine (dose: NR)
Intervention 2: NPH (dose: NR)
Injection frequency: Detemir (twice daily); NPH (twice daily); Glargine (once daily)

Population

Population: Adults with Type 1 Diabetes
Analysis 1 characteristics: Mean age: 39; Male: 63%; Duration of diabetes (years): 15; BMI (kg/m2): 24.9; HbA1c: 8.38; Weight: NR
Analysis 2 characteristics: Mean age: 40.2; Male: 51.3%; Duration of diabetes (years): 17; BMI (kg/m2): 25.5; HbA1c (% points): 8.84; Weight: NR

Data sources

Resource use:
Baseline/natural history: Analysis 1 was based on 595 type diabetes patients for a clinical trial[75], analysis 2 from clinical trial by Pieber et al[107]
Effectiveness: Extracted from corresponding trial for analysis 1[75] and analysis 2[107]
Costs: Cost of treatment, complications, and medication costs from Medicare. Indirect cost (loss of productivity) based on US specific average salaries from the department of labour. Costs inflated to 2005 prices.
QoL: Qol estimates the default CORE values[2] except in the case of severe hypoglycaemic events which were sourced from Davies et al[108] and non-severe from an existing NICE guideline[81]

Base-case results

Analysis	Insulin	Absolute		Incremental		
		Costs (US$)	QALYs	Costs (US$)	QALYs	ICER
Analysis 1	NPH	254,792	7.32			
	Detemir	260,555	8.018	5,763	0.698	US$ 8,256/ QALY[a]
Analysis 2	Glargine	257,528	7.179			
	Detemir	252,354	7.242	-5,174	0.063	Dominant

Converted to 2005 GBP using conversion factor of 0.71[10]

Analysis	Insulin	Absolute		Incremental		
		Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Analysis 1	NPH	180,296	7.32			
	Detemir	184,374	8.018	4,078	0.698	5,842
Analysis 2	Glargine	182,232	7.179			
	Detemir	178,570	7.242	-3,661	0.063	Dominant

Sensitivity analyses

Deterministic: Model input parameters evaluated include changes in HbA1c, discount rate, duration of treatment effect, and costs for insulin and management of hypoglycaemia for Detemir vs NPH evaluation.
Results most sensitive to changes in HbA1c levels for Detemir vs NPH analysis. Detemir vs Glargine analysis was most sensitive to pharmacy acquisition costs.
Probabilistic: Detemir had probability of 100% and 80% of being cost-effective at a WTP of US$50,000/ QALY when compared to NPH and Glargine respectively.

Comments

Source of funding: Novo Nordisk Inc., Princeton, New Jersey, USA
Limitations: Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; CVD, Cardiovascular disease; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NICE, National Institute for Health and Care Excellence; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; US$, US dollar; WTP, willingness to pay
(g) Recalculated by dividing incremental costs by incremental QALYs as reported ICERs did not tally.

Table 25: Valentine et al (2011)[109]

Valentine et al (2011). Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden.

Study details

Analysis: Cost utility analysis

Approach to analysis: CORE Diabetes model – a lifetime Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables.

Diabetes related complications considered included CVDs, diabetic retinopathy, macula oedema, cataract, hypoglycaemic events (major and minor), ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation

Perspective: Swedish healthcare and societal perspective

Time horizon: 50 years

Discounting: 3%

Interventions

Intervention 1: Detemir (dose: NR)

Intervention 2: NPH (dose: NR)

Injection frequency: NR

Population

Population: Adults with Type 1 Diabetes

Characteristics: Mean age: 35; Male: 54.7%; Duration of diabetes (years): 13; BMI (kg/m2): 24.7; HbA1c (% points): 8.3%; Weight (kg): NR

Data sources

Resource use: Insulin doses based on end of trial information from Bartley et al[40]

Baseline/natural history: Prevalence of pre-existing conditions taken from a cross-sectional study of over 5,000 patients in Sweden[49]

Effectiveness: From a single trial by from Bartley et al[40]

Costs: Insulin, needle and testing kit costs obtained from the dental and pharmaceutical benefits agency. Direct medical costs of complications from SALAR (2006) and previous economic evaluations.

QoL: Derived from UKPDS where possible[42], with information from the Australian Institute of Health and Welfare and a range of other sources[14,43,110] used when the information from the UKPDS was not sufficient. Costs inflated to 2006 prices.

Base-case results

	Absolute		Incremental		
	Costs (SEK)	QALYs	Costs (SEK)	QALYs	ICER
NPH	3,040,022	7.82			
Detemir	2,959,909	8.35	-80,113	0.53	Dominant

Converted to 2006 GBP using conversion factor of 0.076[10]

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
NPH	232,382	7.82			
Detemir	226,258	8.35	-6,124	0.53	Dominant

Sensitivity analyses

Deterministic: Model input parameters evaluated include time horizon, discount rate, magnitude of change in HbA1c, BMI, hypoglycaemic event rates, cohort characteristics and treatment effects of Detemir vs NPH.

Scenario: A scenario where lifetime indirect costs were included was evaluated.

Results most sensitive to treatment effects of Detemir on HbA1c levels and hypoglycaemic events.

Probabilistic: At willingness to pay thresholds of SEK 200,000, SEK 300,000 and SEK 400,000, the probability of detemir being cost-effective rose to 99.3%, 99.9% and 100.0%, respectively

Comments

Source of funding: Novo Nordisk, A/S, Denmark

Limitations: Potentially serious limitations (table 29)

Abbreviations: BMI, body mass index; CVD, Cardiovascular disease; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SALAR, Swedish Association of Local Authorities and Regions; SEK, Swedish Krona; SMGB, self-measured blood measured; WTP, willingness to pay

Table 26: Valentine et al (2012)[111]

Valentine et al (2012). Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type 1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands.

Study details

Analysis: Cost utility analysis

Approach to analysis: An Excel based model to estimate the number of non-severe hypoglycaemic events experienced by patients with Type 1diabetes and calculate the effect of those events on quality-adjusted life expectancy and medical costs over 1 year of treatment

<table>
<tr><th colspan="2">Valentine et al (2012). Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type 1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands.</th></tr>
<tr><td></td><td>Diabetes related complications considered: non-severe hypoglycaemic events (severe, non-severe daytime, non-severe nocturnal)
Perspective: Healthcare payer perspective in Denmark, Sweden, Finland, and Norway
Time horizon: 1 year
Discounting: n/a</td></tr>
<tr><td>Interventions</td><td>Intervention 1: Detemir (dose: 40 IU)
Intervention 2: NPH (dose: 40 IU)
Injection frequency: NR</td></tr>
<tr><td>Population</td><td>Population: Adults with Type 1 Diabetes
Characteristics: NR</td></tr>
<tr><td>Data sources</td><td>Resource use: As defined by the World Health Organisation.
Baseline/natural history: Sourced from UKHSG[27]
Effectiveness: From meta-analysis done by the Canadian Agency for Drugs and Technology in Health[73]
Costs: Insulin prices based on respective national pharmacy prices. Cost of non-severe hypoglycaemic evens assumed to be the price of one SMGB test. All costs were inflated to 2009 prices.
QoL: Disutility from non-severe hypoglycaemic event sourced from a study on individuals with and without diabetes in the UK and Canada by Levy et al[112], measured by the eq-5d tool.</td></tr>
<tr><td>Base-case results</td><td>
<table>
<tr><th></th><th colspan="2">Absolute</th><th colspan="3">Incremental</th></tr>
<tr><th></th><th>Costs (€)</th><th>QALYs</th><th>Costs (€)</th><th>QALYs</th><th>ICER</th></tr>
<tr><td>NPH</td><td>NR</td><td>NR</td><td></td><td></td><td></td></tr>
<tr><td>Detemir</td><td>NR</td><td>NR</td><td>238.72</td><td>0.019</td><td>€12,644/ QALY</td></tr>
</table>
Converted to 2009 GBP using conversion factor of 0.79[10] which was calculated by looking at rates for Finland
<table>
<tr><th></th><th colspan="2">Absolute</th><th colspan="3">Incremental</th></tr>
<tr><th></th><th>Costs (£)</th><th>QALYs</th><th>Costs (£)</th><th>QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>NPH</td><td>NR</td><td>NR</td><td></td><td></td><td></td></tr>
<tr><td>Detemir</td><td>NR</td><td>NR</td><td>189</td><td>0.019</td><td>9,951</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity analyses</td><td>Deterministic: Model input parameters evaluated included treatment effects of Detemir vs NPH, cost of insulin, disutility from hypoglycaemic events.
Results remained robust to changes in input parameters with Detemir remaining cost-effective.
Probabilistic: Detemir had an 86% - 89% probability of being cost-effective at a WTP of €50,000/ QALY</td></tr>
<tr><td>Comments</td><td>Source of funding: Novo Nordisk A/S
Limitations: Very serious limitations (table 29)</td></tr>
</table>

Abbreviations: BMI, body mass index; eq-5d, Euro-qol five dimensions, GBP, Great British Pounds; HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IU, international units; NPH, neutral protamine Hagedorn; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

Table 27: Warren et al (2004)[113]

<table>
<tr><th colspan="2">Warren et al (2004). Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine.</th></tr>
<tr><td>Study details</td><td>Analysis: Cost utility analysis
Approach to analysis: Model developed to predict the cost and QALYs associated with hypoglycaemic complications over a period of 9 years. Other long-term complications only considered in alternative analysis.
Diabetes related complications considered: Severe and symptomatic hypoglycaemic events
Perspective: UK National Health Service
Time horizon: 9 years
Discounting: NR</td></tr>
<tr><td>Interventions</td><td>Intervention 1: Glargine (dose: NR)
Intervention 2: NPH (dose: NR)
Injection frequency: NR</td></tr>
<tr><td>Population</td><td>Population: Adults with Type 1 Diabetes
Characteristics: Mean age: 27; Male: 52.5%; Duration of diabetes (years): 5.6; BMI (kg/m2): NR; HbA1c (% points): 8.87; Weight (kg): NR</td></tr>
</table>

Warren et al (2004). Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine.

Data sources

Resource use: NR

Baseline/natural history: Baseline hypoglycaemic events sourced from Pampanelli et al[114] and DCCT trial[59]

Effectiveness: Sourced from a single trial by Ratner et al[115]. In an alternative analysis where long-term differences in HbA1c levels were considered using results from Pieber et al[116]

Costs: NHS reference costs 2002, PSSRU 2001, and industry submission to this HTA. Costs inflated to 2001 prices.

QoL: QoI associated with hypoglycaemia events taken from Nordfeldt et al[117]. Effects on QoL by long-term complications assumed to be the same as industry submission.

Base-case results

	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)[1]	QALYs	ICER (£/QALY)[1]
NPH	1,738	NR			
Glargine	2,311 – 2,554	NR	573 – 816	NR	3,496 - 4,978

Sensitivity analyses

Deterministic: Model input parameters evaluated include discount rate, treatment effects of Glargine vs NPH for hypoglycaemic events and HbA1c levels,

Scenario Analysis: Scenario performed where no utility gained was assumed from reduced fear of hypoglycaemic events.

Results most sensitive to scenario analysis described above.

Probabilistic: NR

Comments

Source of funding: NIHR HTA

Limitations: Very serious limitations (table 29)

Abbreviations: BMI, body mass index; DCCT, Diabetes Control and Complications Trial; eq-5d, Euro-qol five dimensions, HbA1c, glycosylated haemoglobin; HTA, Health Technology Assessment; ICER, incremental cost-effectiveness ratio; IU, international units; NIHR, National Institute of Health Research; NPH, neutral protamine Hagedorn; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; QoL, quality of life; SMGB, self-measured blood measured; WTP, willingness to pay

[1]Results from 2 alternative scenarios

Table 28: Applicability checklist

Study	1.1 Is the study population appropriate for the review question?	1.2 Are the interventions appropriate for the review question?	1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	1.4 Is the perspective for costs appropriate for the review question?	1.5 Is the perspective for outcomes appropriate for the review question?	1.6 Are all future costs and outcomes discounted appropriately?	1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome?	1.8 Overall judgement
Cameron et al (2009)[1]	Unclear	Partly	Partly (Canadian study with a third-party payer perspective)	Yes	Yes	Partly (dr: 5%)	Yes (primarily eq-5d, with some sources using TTO and standard gamble techniques)	Partially applicable
Dawoud et al (2017)[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes (primarily eq-5d with other measures involved in default CORE model values)	Directly applicable
Ericcson et al (2012)[15]	Unclear	Partly	Partly (Swedish study, but in the perspective of their national health system)	Yes	Yes	Yes[1]	Partly (QoL effects from SMGB tests based on eq-5d, others based on TTO questionnaire)	Partially applicable
Evans et al (2015)[21]	Unclear	Partly	Yes	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable
Evans et al (2015)[25]	Yes	Partly	Yes	Unclear (sources of costs not reported, only that costs were UK derived)	Yes	Yes	Unclear (sources of QoL not reported)	Partially applicable
Evans et al (2017)[26]	Unclear	Partly	Yes	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable
Evans et al (2018)[30]	Unclear	Partly	Yes	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable
Grima et al (2007)[32]	Partly (mean age of 27)	Partly	Partly (Canadian study with Canadian public payer perspective)	Yes	Yes	Partly (dr: 5%)	Yes (primarily eq-5d with some sources using the Self-Administered Quality of Well Being index measurement tool)	Partially applicable

Study	1.1 Is the study population appropriate for the review question?	1.2 Are the interventions appropriate for the review question?	1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	1.4 Is the perspective for costs appropriate for the review question?	1.5 Is the perspective for outcomes appropriate for the review question?	1.6 Are all future costs and outcomes discounted appropriately?	1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome?	1.8 Overall judgement
Gschwend et al (2009)[39]	Yes	Partly	Partly (third party payer perspective in 5 European countries)	Yes	Yes	Partly (dr:3% - 6% (country specific))	Yes (primarily eq-5d)	Partially applicable
Haldrup et al (2020)[44])	Yes	Partly	Partly (Italian study with a healthcare payer perspective)	Yes	Yes	Partly (dr: 3%)	Yes (primarily eq5d)	Partially applicable
Hallin et al (2017)[47]	Yes	Partly	Partly (Swedish study)	Yes	Yes	Partly (dr: 3%)	Yes (primarily eq5d, with some of the sources used using SF-36 measurement tool)	Partially applicably
Lalic et al (2018)[54]	Unclear	Partly	Partly (Serbian setting in the perspective of the Serbian insurance fund)	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable
McEwan et al (2007)[57]	Partly (mean age of 27)	Partly	Yes	Yes	Yes	Yes	Yes (eq-5d)	Partially applicable
Mezquita-Raya et al (2017)[69]	Unclear	Partly	Partly (Spanish study, but in the perspective of their national health system)	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable
Morales et al (2015)[72]	Unclear	Partly	Partly (Spanish study, but in the perspective of their national health system)	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable
Palmer et al (2004)[74]	Yes	Partly	Yes	Yes	Yes	Yes	Yes (primarily eq-5d)	Partially applicable
Palmer et al (2007)[82]	Yes	Partly	Yes	Yes	Yes	Yes	Yes (eq-5d)	Partially applicable
Pedersen-Bjergaard et al (2016)[84]	Partly (mean age of 54)	Partly	Partly (Danish study, with clinical costs included. These costs do not differ substantially from a public healthcare perspective)	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable

Study	1.1 Is the study population appropriate for the review question?	1.2 Are the interventions appropriate for the review question?	1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	1.4 Is the perspective for costs appropriate for the review question?	1.5 Is the perspective for outcomes appropriate for the review question?	1.6 Are all future costs and outcomes discounted appropriately?	1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome?	1.8 Overall judgement
Pfohl et al (2012)[88]	Yes	Partly	Partly (perspective of the German Statutory Health Insurance (mainly third-party payer))	Yes	Yes	Partly (dr: 3%)	Yes (eq-5d)	Partially applicable
Pollock et al (2017)[95]	Unclear	Partly	Partly (Danish setting in the perspective of the Danish healthcare payer)	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable
Pollock et al (2018)[96]	Unclear	Partly	Yes	Yes	Yes	Yes[1]	Yes	Partially applicable
Russel-Szymczyk et al (2019)[99]	Unclear	Partly	Partly (Bulgarian study with national health insurance payer)	Yes	Yes	Partly (dr:3%)	Yes (eq-5d)	Partially applicable.
Tunis et al (2009)[102]	Partly (mean age of 27)	Partly	Partly (Canadian study with Canadian provincial govt perspective)	Yes	Yes	Partly (dr: 5%)	Unclear (lack of clarity over which inputs from previous economic evaluation[105])	Partially applicable
Valentine et al (2006)[106]	Yes	Partly	No (US health system perspective)	Yes (also includes loss in productivity costs)	Yes	Partly (dr: 3%)	Yes (primarily eq-5d except in cases where default CORE values)	Partially applicable
Valentine et al (2011)[109]	Yes	Partly	Partly (Swedish study, but in the perspective of their national health system. Also includes societal perspective)	Yes (societal costs in the form of loss in productivity has also been included)	Yes	Partly (dr: 3%)	Yes (most QoL measures sourced from UKPDS which used eq-5d)	Partially applicable.
Valentine et al (2012)[111]	Unclear	Partly	Partly (set in 4 European countries, but in the perspective of the national healthcare payer)	Yes	Yes	Yes[1]	Yes (eq-5d)	Partially applicable
Warren et al (2004)[111]	Partly (mean age of 25)	Partly	Yes	Yes	Yes	Unclear (not reported)	Unclear (QoL impact from long-term complications	Partially applicable

Study	1.1 Is the study population appropriate for the review question?	1.2 Are the interventions appropriate for the review question?	1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	1.4 Is the perspective for costs appropriate for the review question?	1.5 Is the perspective for outcomes appropriate for the review question?	1.6 Are all future costs and outcomes discounted appropriately?	1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome?	1.8 Overall judgement
							sourced from industry submission which is not available)	

Abbreviations: dr, discount rate; eq-5d, Euro-quality of life five dimensions; NICE, National Institute for Health and Care Excellence; QALYs, quality adjusted life years; SF-36, short form 36; TTO, time trade-off; UKPDS, UK Prospective Diabetes Study
[1]1-year time horizon, so no discounting performed

Table 29: Limitations checklist

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
Cameron et al (2009)[1]	Yes	Yes	Yes	Partly (sourced from various sources based on literature review)	Yes	Yes	Partly (sourced from an endocrinologist)	Yes	Yes	Yes	Yes	Minor limitations
Dawoud et al (2017)[11]	Yes	Yes	Partly (No costs or impact on QoL assumed for minor hypoglycaemic events. Event rates for minor hypoglycaemic events also nor reported)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Minor limitations
Ericcson et al (2012)[15]	Yes	Partly (time horizon of 1 year)	Yes (only hypoglycaemic events included)	Partly (from Swedish patients in observational study)	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Evans et al (2015)[21]	Yes	Partly (time horizon of 1 year)	Yes (only hypoglycaemic events included)	Partly (taken from clinical trial data)	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor Limitations.
Evans et al (2015)[25]	Yes	Yes	Yes	Partly - taken from clinical trial data of	Partly (sourced from clinical trial	Unclear (sources of	Yes	Unclear (sources of	Yes	Partly (No PSA results reported,	No	Very serious limitations

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
				35T1D patients	data of 35 T1D patients)	costs not reported)		costs not reported)		only 2 variables varied in 1-way sensitivity analysis)		
Evans et al (2017)[26]	Yes	Partly (time horizon of 1 year)	Yes (only hypoglycaemic events included)	Partly (from UKHSG)	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor Limitations
Evans et al (2018)[30]	Yes	Partly (time horizon of 1 year)	Yes (only hypoglycaemic events included)	Partly - *taken from a single trial (SWITCH))	Partly (sourced from a single trial (SWITCH))	Yes	Partly (sourced from single trial - SWITCH)	Yes	Yes	Yes	No	Potentially serious limitations
Grima et al (2007)[32]	Yes	Yes	Yes	Partly (from various sources, but not from a systematic review)	Partly (not from a meta-analysis – single study)	Yes	Partly (not from a meta-analysis)	Yes	Yes	Partly (no PSA reported)	No	Very serious limitations
Gschwend et al (2009)[39]	Yes	Yes	Partly (minor hypoglycaemic events not considered)	Partly (from various sources, but not from a systematic review)	Unclear	Yes	Unclear	Yes	Yes	Yes	No	Very serious limitations
Haldrup et al (2020)[44])	Yes	Yes	Yes	Partly (sourced from EU-TREAT study)	Partly (sourced from EU-TREAT study)	Yes	Partly (sourced from EU-TREAT study)	Yes	Yes	Yes	No	Potentially serious limitations

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
Hallin et al (2017)[47]	Yes	Yes	Yes	Partly (baseline values not sourced after conducting a systematic review)	Partly (not sourced after conducting a systematic review)	Yes	Partly (from a single study)	Yes	Yes	Partly (PSA not performed)	No	Potentially serious limitations
Lalic et al (2018)[54]	Yes	Partly (time horizon of 1 year)	Yes (limited to hypoglycaemic events)	Partly (sourced from largescale study in 7 European countries)	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor Limitations
McEwan et al (2007)[57]	Yes	Yes	Yes	Partly (Baseline rates from DCCT trial)	Partly (sourced from unpublished meta-analysis by Sanofi Aventis)	Yes	Unclear	Yes	Yes	Partly (PSA not performed)	No	Very serious limitations
Mezquita-Raya et al (2017)[69]	Yes	Partly (time horizon of 1 year)	Yes (limited to hypoglycaemia events)	Partly (not take from a meta-analysis but reflective Spanish observational study)	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor Limitations
Morales et al (2015)[72]	Yes	Partly (time horizon of 1 year)	Partly (limited to minor hypoglycaemic events)	Partly (sourced from UKHSG)	Yes	Yes	Partly (as indicated by WHO)	Yes	Yes	Yes	No	Potentially serious limitations

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
Palmer et al (2004)[74]	Yes	Yes	Yes	Partly (baseline characteristics from a range of studies)	Yes	Yes	Unclear	Yes	Yes	Yes	No	Potentially serious limitations
Palmer et al (2007)[82]	Yes	Yes	Yes	Partly (baseline characteristics from trial data)	Partly (sourced from a single trial)	Yes	Partly (from end of trial data in a single trial)	Yes	Yes	Yes	No	Potentially serious limitations
Pedersen-Bjergaard et al (2016)[84]	Yes	Partly (time horizon of 1 year)	Partly (limited to hypoglycaemic events)	Partly (sourced from a single trial)	Partly (sourced from HypoAnna study)	Partly (sourced from HypoAnna study)	Partly (from a single trial)	Yes	Yes	Partly (no PSA performed. One-way sensitivity analysis done for 2 input parameters)	No	Very serious limitations
Pfohl et al (2012)[88]	Yes	Yes	Yes	Partly (from UKPDS and DCCT)	Yes	Yes	Unclear	Yes	Yes	Yes	No	Potentially serious limitations
Pollock et al (2017)[95]	Yes	Partly (time horizon of 1 year)	Yes (limited to hypoglycaemic events)	Partly (sourced from a single Danish study)	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor Limitations
Pollock et al (2018)[96]	Yes	Partly (time horizon of 1 year)	Partly (limited to non-severe hypoglycaemic events (not split by time of day))	Partly (sourced from a single UK specific study)	Yes	Yes	Partly (sourced from DAFNE)	Yes	Yes	Yes	No	Potentially serious limitations

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
Russel-Szymczyk et al (2019)[99]	Yes	Partly (time horizon of 1 year)	Partly- outcomes other than minor hypoglycaemic events not included	Partly (sourced from UKHSG)	Yes	Yes	Partly (resource use for Glargine from clinical practise and dose ratio from meta-analysis)	Yes	Yes	Yes	No	Potentially serious limitations
Tunis et al (2009)[102]	Yes	Yes	Yes	Partly (from a single cohort)	Partly (from a single trial)	Yes	Unclear	Yes	Yes	Partly (insufficient parameters considered in deterministic sensitivity analysis)	No	Potentially serious limitations
Valentine et al (2006)[106]	Yes	Yes (35 years)	Yes	Partly (from a single RCT)	Partly (from a single RCT)	Yes	Unclear	Yes	Yes	Yes	No	Potentially serious limitations
Valentine et al (2011)[109]	Yes	Yes	Partly (unclear as to whether non severe hypoglycaemic events are considered)	Partly (baseline characteristics taken from Swedish observational study)	Partly (from a single trial)	Yes (Indirect societal costs are also included)	Partly (end of trial data)	Yes	Yes	Yes	No	Potentially serious limitations
Valentine et al (2012)[111]	Yes	Partly (time horizon of 1 year)	Partly (only minor hypoglycaemic events are considered	Partly (from UK based observational study)	Yes	Yes	Partly (WHO recommendation)	Yes	Yes	Yes	No	Very serious limitations

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
Warren et al (2004)[111]	Yes	Partly (time horizon of 9 years)	Yes	Partly (sourced from a single trials)	Partly (sourced from a single trial)	Yes	Unclear	Yes	Yes	Partly – PSA not reported	Yes	Very serious limitations

Abbreviations: DCCT, Diabetes Control and Complications Trial; EU-TREAT, EUropean TREsiba Audit; HbA1c, glycosylated haemoglobin; RCT, PSA, probabilistic sensitivity analysis; Randomized control trial; UKHSG, UK Hypoglycaemia Study Group; UKPDS, UK Prospective Diabetes Study

Bibliography

1. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. *C Can Med Assoc J*. 2009;180(4):400-407. http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22009100602/frame.html

2. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and costeffectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin*. 2004;20(sup1):S5-S26.

3. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *Cmaj*. 2009;180(4):385-397.

4. O'Reilly D, Hopkins R, Blackhouse G, Clarke P, Hux J, Guan J. *Development of an Ontario Diabetes Economic Model (ODEM) and Application to a Multidisciplinary Primary Care Diabetes Management Program*. Programs for Assessment of Technology in Health; 2007.

5. Hart HE, Redekop WK, Berg M, Bilo HJG, Meyboom-de Jong B. Factors that predicted change in health-related quality of life were identified in a cohort of diabetes mellitus type 1 patients. *J Clin Epidemiol*. 2005;58(11):1158-1164.

6. Economics I of H, Manns B. *Quality of Life in Patients with End-Stage Renal Disease over Time: The Impact of Dialysis Modality and Other Important Determinants*. Institute of Health Economics; 2002.

7. Manns B, Tonelli M, Shrive F. Sevelamer in patients with end-stage renal disease: a systematic review and economic evaluation. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2006. *Technol Rep*. (71).

8. Ray JA, Valentine WJ, Secnik K, et al. Review of the cost of diabetes complications in Australia, Canada, France, Germany, Italy and Spain. *Curr Med Res Opin*. 2005;21(10):1617-1629.

9. Quality A for HR and. Calculating the US population-based EQ-5D™ index score. Published online 2005.

10. Organisation for Economic Co-operation and Development (OECD). Purchasing Power Parities and exchange rates. Published 2019. Accessed August 3, 2020. https://stats.oecd.org/Index.aspx?DataSetCode=PPP2017

11. Dawoud D, Fenu E, Higgins B, Wonderling D, Amiel SA. Basal Insulin Regimens for Adults with Type 1 Diabetes Mellitus: A Cost-Utility Analysis. *Value Heal*. 2017;20(10):1279-1287. doi:10.1016/j.jval.2017.05.021

12. Nathan DM, Zinman B, Cleary PA, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2. *Arch Intern Med*. 2009;169(14):1307.

13. Hammer M, Lammert M, Mejías SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. *J Med Econ*. 2009;12(4):281-290.

14. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. *Curr Med Res Opin*. 2006;22(8):1523-1534.

15. Ericsson Å, Pollock RF, Hunt B, Valentine WJ. Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. *J Med Econ*. 2013;16(12):1442-1452. doi:10.3111/13696998.2013.852099

16. Östenson CG, Geelhoed-Duijvestijn P, Lahtela J, Weitgasser R, Markert Jensen M, Pedersen-Bjergaard U. Self-reported non-severe hypoglycaemic events in Europe. *Diabet Med*. 2014;31(1):92-101.

17. Jönsson L, Bolinder B, Lundkvist J. Cost of hypoglycemia in patients with Type 2 diabetes in Sweden. *Value Heal*. 2006;9(3):193-198.

18. Geelhoed-Duijvestijn PH, Pedersen-Bjergaard U, Weitgasser R, Lahtela J, Jensen MM, Östenson C-G. Effects of patient-reported non-severe hypoglycemia on healthcare resource use, work-time loss, and wellbeing in insulin-treated patients with diabetes in seven European countries. *J Med Econ*. 2013;16(12):1453-1461.

19. Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. *Health Qual Life Outcomes*. 2013;11(1):90.

20. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. *bmj*. 2008;336(7654):1177-1180.

21. Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with type 1 diabetes mellitus in the UK. *J Med Econ*. 2015;18(1):56-68. doi:10.3111/13696998.2014.971160

22. Mathieu C, Hollander P, Miranda-Palma B, et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab*. 2013;98(3):1154-1162.

23. Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1489-1497.

24. Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. *Diabetes Ther*. 2014;5(2):435-446.

25. Evans M, McEwan P, Foos V. Insulin degludec early clinical experience: Does the promise from the clinical trials translate into clinical practice-a case-based evaluation. *J Med Econ*. 2015;18(2):96-105. doi:10.3111/13696998.2014.975234

26. Evans M, Chubb B, Gundgaard J. Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Adults with Type 1 and Type 2 Diabetes Mellitus. *Diabetes Ther*. 2017;8(2):275-291. doi:10.1007/s13300-017-0236-9

27. Group UKHS. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*. 2007;50(6):1140-1147.

28. Ratner RE, Gough SCL, Mathieu C, et al. Hypoglycaemia risk with insulin degludec

compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes, Obes Metab*. 2013;15(2):175-184.

29. Chubb B, Tikkanen C. The cost of non-severe hypoglycaemia in Europe. *Value Heal*. 2015;18(7):A611.

30. Evans M, Mehta R, Gundgaard J, Chubb B. Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting. *Diabetes Ther*. 2018;9(5):1919-1930. doi:10.1007/s13300-018-0478-1

31. Lane W, Bailey TS, Gerety G, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. *Jama*. 2017;318(1):33-44.

32. Grima DT, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. *Pharmacoeconomics*. 2007;25(3):253-266. doi:10.2165/00019053-200725030-00007

33. Porcellati F, Rossetti P, Pampanelli S, et al. Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med*. 2004;21(11):1213-1220.

34. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Bmj*. 2000;321(7258):405-412.

35. O'Brien JA, Patrick AR, Caro JJ. Cost of managing complications resulting from type 2 diabetes mellitus in Canada. *BMC Health Serv Res*. 2003;3(1):7.

36. Coyle D, Palmer AJ, Tam R. Economic evaluation of pioglitazone hydrochloride in the management of type 2 diabetes mellitus in Canada. *Pharmacoeconomics*. 2002;20(1):31-42.

37. Coffey JT, Brandle M, Zhou H, et al. Valuing health-related quality of life in diabetes. *Diabetes Care*. 2002;25(12):2238-2243.

38. UK Prosepective Diabetes study Group. Quality of life in type 2 diabetic patients is affected by complications bu-t not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). UK Prospective Diabetes Study Group. *Diabetes Care*. 1999;22(7):1125-1136.

39. Gschwend MH, Aagren M, Valentine WJ. Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. *J Med Econ*. 2009;12(2):114-123. doi:10.3111/13696990903080344

40. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to neutral protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal–bolus regimen with insulin aspart at meals: a 2-year randomized controlled trial. *Diabet Med*. 2008;25(4):442-449.

41. Mathers C, Vos T, Stevenson C. *The Burden of Disease and Injury in Australia*. Australian Institute of Health and Welfare; 1999.

42. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Med Decis Mak*. 2002;22(4):340-349.

43. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care*. Published online 2000:583-637.

44. Haldrup S, Lapolla A, Gundgaard J, Wolden ML. Cost-effectiveness of switching to insulin degludec from other basal insulins in real-world clinical practice in Italy. *J Med Econ*. 2020;23(3):271-279.

45. Giorda CB, Rossi MC, Ozzello O, et al. Healthcare resource use, direct and indirect costs of hypoglycemia in type 1 and type 2 diabetes, and nationwide projections. Results of the HYPOS-1 study. *Nutr Metab Cardiovasc Dis*. 2017;27(3):209-216.

46. Freemantle N, Evans M, Christensen T, Wolden ML, Bjorner JB. A comparison of health-related quality of life (health utility) between insulin degludec and insulin glargine: a meta-analysis of phase 3 trials. *Diabetes, Obes Metab*. 2013;15(6):564-571.

47. Landstedt-Hallin L, Gundgaard J, Ericsson Å, Ellfors-Zetterlund S. Cost-effectiveness of switching to insulin degludec from other basal insulins: evidence from Swedish real-world data. *Curr Med Res Opin*. 2017;33(4):647-655.

48. Landstedt-Hallin L. Changes in HbA1c, insulin dose and incidence of hypoglycemia in patients with type 1 diabetes after switching to insulin degludec in an outpatient setting: an observational study. *Curr Med Res Opin*. 2015;31(8):1487-1493.

49. FÄRNKVIST LM, LUNDMAN BM. Outcomes of diabetes care: a population-based study. *Int J Qual Heal care*. 2003;15(4):301-307.

50. Lind M, Bounias I, Olsson M, Gudbjörnsdottir S, Svensson A-M, Rosengren A. Glycaemic control and incidence of heart failure in 20 985 patients with type 1 diabetes: an observational study. *Lancet*. 2011;378(9786):140-146.

51. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Gudbjörnsdottir S, Register SND. A new model for 5-year risk of cardiovascular disease in Type 1 diabetes; from the Swedish National Diabetes Register (NDR). *Diabet Med*. 2011;28(10):1213-1220.

52. Jonasson JM, Ye W, Sparén P, Apelqvist J, Nyrén O, Brismar K. Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care*. 2008;31(8):1536-1540.

53. Lauridsen JT, Lønborg J, Gundgaard J, Jensen HH. Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. *Qual Life Res*. 2014;23(9):2645-2650.

54. Lalić N, Russel-Szymczyk M, Culic M, Tikkanen CK, Chubb B. Cost-Effectiveness of Insulin Degludec Versus Insulin Glargine U100 in Patients with Type 1 and Type 2 Diabetes Mellitus in Serbia. *Diabetes Ther*. 2018;9(3):1201-1216. doi:10.1007/s13300-018-0426-0

55. Heller SR, Frier BM, Hersløv ML, Gundgaard J, Gough SCL. Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources. *Diabet Med*. 2016;33(4):471-477.

56. Organisation for Economic Co-operation and Development (OECD). 2017 Purchasing Power Parities Benchmark results. Published 2017. Accessed August 3, 2020. https://stats.oecd.org/Index.aspx?DataSetCode=PPP2017

57. McEwan P, Poole CD, Tetlow T, Holmes P, Currie CJ. Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK. *Curr Med Res Opin Suppl*. 2007;23(1). doi:10.1185/030079906X167561

58. Palmer AJ, Weiss C, Sendi PP, et al. The cost-effectiveness of different management

strategies for type I diabetes: a Swiss perspective. *Diabetologia*. 2000;43(1):13-26.

59. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.

60. Moss SE, Klein R, Klein BEK. The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Intern Med*. 1992;152(3):610-616.

61. Group DRSR. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. *Ophthalmology*. 1981;88(7):583-600.

62. Faglia E, Favales F, Morabito A. New ulceration, new major amputation, and survival rates in diabetic subjects hospitalized for foot ulceration from 1990 to 1993: a 6.5-year follow-up. *Diabetes Care*. 2001;24(1):78-83.

63. Bild DE, Selby J V, Sinnock P, Browner WS, Braveman P, Showstack JA. Lower-extremity amputation in people with diabetes: epidemiology and prevention. *Diabetes Care*. 1989;12(1):24-31.

64. Leese GP, Wang J, Broomhall J, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care*. 2003;26(4):1176-1180.

65. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabet Med*. 2003;20(6):442-450.

66. McEwan P, Dixon S, Baboolal K, Conway P, Currie CJ. Evaluation of the cost effectiveness of sirolimus versus tacrolimus for immunosuppression following renal transplantation in the UK. *Pharmacoeconomics*. 2006;24(1):67-79.

67. Morgan CL, McEwan P, Morrissey M, Peters JR, Poole C, Currie CJ. Characterization and comparison of health-related utility in people with diabetes with various single and multiple vascular complications. *Diabet Med*. 2006;23(10):1100-1105.

68. Currie CJ, McEwan P, Peters JR, Patel TC, Dixon S. The routine collation of health outcomes data from hospital treated subjects in the Health Outcomes Data Repository (HODaR): descriptive analysis from the first 20,000 subjects. *Value Heal*. 2005;8(5):581-590.

69. Mezquita-Raya P, Darbà J, Ascanio M, Ramírez de Arellano A. Cost-effectiveness analysis of insulin degludec compared with insulin glargine u100 for the management of type 1 and type 2 diabetes mellitus–from the Spanish National Health System perspective. *Expert Rev Pharmacoeconomics Outcomes Res*. 2017;17(6):587-595. doi:10.1080/14737167.2017.1345628

70. Orozco-Beltrán D, Mezquita-Raya P, De Arellano AR, Galán M. Self-reported frequency and impact of hypoglycemic events in Spain. *Diabetes Ther*. 2014;5(1):155-168.

71. Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. *Value Heal*. 2011;14(5):665-671.

72. Morales C, de Luis D, de Arellano AR, Ferrario MG, Lizán L. Cost-Effectiveness Analysis of Insulin Detemir Compared to Neutral Protamine Hagedorn (NPH) in Patients with Type 1 and Type 2 Diabetes Mellitus in Spain. *Diabetes Ther*.

2015;6(4):593-610. doi:10.1007/s13300-015-0143-x

73. (CADTH CA for D and T in H. Long-acting insulin analogues for the treatment of diabetes mellitus: meta-analyses of clinical outcomes. *CADTH Technol Overv*. 2010;1(1).

74. Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen KU. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. *Curr Med Res Opin*. 2004;20(11):1729-1746.

75. Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall M-A. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia*. 2004;47(4):622-629.

76. UK Prosepective Diabetes study Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *Bmj*. 1998;317(7160):720-726.

77. Currie CJ, Morgan CLL, Peters JR. The epidemiology and cost of inpatient care for peripheral vascular disease, infection, neuropathy, and ulceration in diabetes. *Diabetes Care*. 1998;21(1):42-48.

78. Ghatnekar O, Persson U, Willis M, Ödegaard K. Cost effectiveness of Becaplermin in the treatment of diabetic foot ulcers in four European countries. *Pharmacoeconomics*. 2001;19(7):767-778.

79. James M, Turner DA, Broadbent DM, Vora J, Harding SP. Cost effectiveness analysis of screening for sight threatening diabetic eye disease. *Bmj*. 2000;320(7250):1627-1631.

80. Scuffham P, Carr L. The cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections for the management of diabetes. *Diabet Med*. 2003;20(7):586-593.

81. Excellence NI for C. Guidance on the use of long-acting insulin analogues for the treatment of diabetes insulin glargine. *London NICE*. Published online 2002.

82. Palmer AJ, Valentine WJ, Ray JA, et al. An economic assessment of analogue basal–bolus insulin versus human basal–bolus insulin in subjects with type 1 diabetes in the UK. *Curr Med Res Opin*. 2007;23(4):895-901.

83. Currie CJ, Gale EAM, Poole CD. Estimation of primary care treatment costs and treatment efficacy for people with type 1 and type 2 diabetes in the United Kingdom from 1997 to 2007. *Diabet Med*. 2010;27(8):938-948.

84. Pedersen-Bjergaard U, Kristensen PL, Nørgaard K, et al. Short-term cost-effectiveness of insulin detemir and insulin aspart in people with type 1 diabetes who are prone to recurrent severe hypoglycemia. *Curr Med Res Opin*. 2016;32(10):1719-1725. doi:10.1080/03007995.2016.1205006

85. Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. *lancet Diabetes Endocrinol*. 2014;2(7):553-561.

86. Kristensen PL, Pedersen-Bjergaard U, Beck-Nielsen H, et al. A prospective randomised cross-over study of the effect of insulin analogues and human insulin on

the frequency of severe hypoglycaemia in patients with type 1 diabetes and recurrent hypoglycaemia (the HypoAna trial): study rationale and design. *BMC Endocr Disord*. 2012;12(1):1-7.

87. Agesen RM, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type 1 diabetes prone to severe hypoglycaemia: The HypoAna trial. *Diabetes Metab*. 2016;42(4):249-255.

88. Pfohl M, Schädlich PK, Dippel FW, Koltermann KC. Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. *J Med Econ*. 2012;15(SUPPL. 2):14-27. doi:10.3111/13696998.2012.713879

89. Cardiff Research Consortium (CRC) Limited. LANTUS health outcomes model - Model manual. Published online 2008.

90. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR, Group UKPDS (UKPDS). The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci*. 2001;101(6):671-679.

91. Mullins P, Sharplin P, Yki-Jarvinen H, Riddle MC, Haring H-U. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven Phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther*. 2007;29(8):1607-1619.

92. Mittendorf T, Smith-Palmer J, Timlin L, Happich M, Goodall G. Evaluation of exenatide vs. insulin glargine in type 2 diabetes: cost-effectiveness analysis in the German setting. *Diabetes, Obes Metab*. 2009;11(11):1068-1079.

93. Clarke PM, Gray AM, Briggs A, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia*. 2004;47(10):1747-1759.

94. Lee AJ, Morgan CL, Conway P, Currie CJ. Characterisation and comparison of health-related quality of life for patients with renal failure. *Curr Med Res Opin*. 2005;21(11):1777-1783.

95. Pollock RF, Tikkanen CK. A short-term cost-utility analysis of insulin degludec versus insulin glargine U100 in patients with type 1 or type 2 diabetes in Denmark. *J Med Econ*. 2017;20(3):213-220.

96. Pollock RF, Chubb B, Valentine WJ, Heller S. Evaluating the cost-effectiveness of insulin detemir versus neutral protamine hagedorn insulin in patients with type 1 or type 2 diabetes in the UK using a short-term modeling approach. *Diabetes, Metab Syndr Obes Targets Ther*. 2018;11:217-226. doi:10.2147/DMSO.S156739

97. Gillespie P, O'Shea E, O'Hara MC, Dinneen SF, Group IDS. Cost effectiveness of group follow-up after structured education for type 1 diabetes: a cluster randomised controlled trial. *Trials*. 2014;15(1):227.

98. Frier BM, Jensen MM, Chubb BD. Hypoglycaemia in adults with insulin-treated diabetes in the UK: self-reported frequency and effects. *Diabet Med*. 2016;33(8):1125-1132.

99. Russel-Szymczyk M, Valov V, Savova A, Manova M. Cost-effectiveness of insulin degludec versus insulin glargine U100 in adults with type 1 and type 2 diabetes mellitus in Bulgaria. *BMC Endocr Disord*. 2019;19(1):1-10. doi:10.1186/s12902-019-

0460-6

100. Doneva M, Valov V, Borisova A-M, et al. Comparative analysis of the cost of insulin treated patients in Bulgaria. *Biotechnol Biotechnol Equip*. 2013;27(2):3748-3752.

101. Brod M, Rana A, Barnett AH. Impact of self-treated hypoglycaemia in type 2 diabetes: a multinational survey in patients and physicians. *Curr Med Res Opin*. 2012;28(12):1947-1958.

102. Tunis SL, Minshall ME, Conner C, et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: Modeling analysis. *Curr Med Res Opin*. 2009;25(5):1273-1284. doi:10.1185/03007990902869169

103. Group DC and CT of DI and C (DCCT/EDIC) SR. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353(25):2643-2653.

104. Caro J, Migliaccio-Walle K, Ishak KJ, Proskorovsky I. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord*. 2005;5(1):14.

105. Canadian Agency for Drugs and Technologies in Health. An economic evaluation of insulin analogues for the treatment of patients with type 1 and type 2 diabetes mellitus in Canada. *Optim Ther Report-COMPUS*. 2008;2(4).

106. Valentine WJ, Palmer AJ, Erny-Albrecht KM, et al. Cost-effectiveness of basal insulin from a US health system perspective: Comparative analyses of detemir, glargine and NPH. *Adv Ther*. 2006;23(2):191-207. doi:10.1007/BF02850126

107. Pieber TR, Treichel HC, Robertson LI, Mordhorst L, Gall MA. Insulin detemir plus insulin aspart is associated with less risk of major as well as nocturnal hypoglycaemia than insulin glargine plus insulin aspart at comparable levels of glycaemic control in type 1 diabetes. In: *Diabetologia*. Vol 48. SPRINGER 233 SPRING STREET, NEW YORK, NY 10013 USA; 2005:A92-A92.

108. Davis RE, Wittrup-Jensen KU, Peters JR, Morrissey M, Currie CJ. The impact on health-related quality of life (EQ-5D (index)) in people with type 1 diabetes who experience severe hypoglycaemia. In: *Diabetologia*. Vol 48. SPRINGER 233 SPRING STREET, NEW YORK, NY 10013 USA; 2005:A292-A293.

109. Valentine WJ, Aagren M, Haglund M, Ericsson Å, Gschwend MH. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden. *Scand J Public Health*. 2011;39(1):79-87.

110. Carrington AL, Mawdsley SK V, Morley M, Kincey J, Boulton AJM. Psychological status of diabetic people with or without lower limb disability. *Diabetes Res Clin Pract*. 1996;32(1-2):19-25.

111. Valentine WJ, Jendle J, Saraheimo M, Thorsteinsson B, Pollock RF, Lammert M. Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands. *Diabet Med*. 2012;29(3):303-312. doi:10.1111/j.1464-5491.2011.03461.x

112. Levy AR, Christensen TLU, Johnson JA. Utility values for symptomatic non-severe hypoglycaemia elicited from persons with and without diabetes in Canada and the

United Kingdom. *Health Qual Life Outcomes*. 2008;6(1):73.

113. Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. *Health Technol Assess (Rockv)*. 2004;8(45). doi:10.3310/hta8450

114. Pampanelli S, Fanelli C, Lalli C, et al. Long-term intensive insulin therapy in IDDM: effects on HbA 1c, risk for severe and mild hypoglycaemia, status of counterregulation and awareness of hypoglycaemia. *Diabetologia*. 1996;39(6):677-686.

115. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. US Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care*. 2000;23(5):639-643.

116. Pieber TR, Eugène-Jolchine I, Derobert E. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. *Diabetes Care*. 2000;23(2):157-162.

117. Nordfeldt S, Jonsson D. Short-term effects of severe hypoglycaemia in children and adolescents with type 1 diabetes. A cost-of-illness study. *Acta Paediatr*. 2001;90(2):137-142.

Appendix N – Health economic model

Details of the health economic model are shown in the economic model report.

Appendix O – Excluded studies

Clinical

Study	Reason
Agesen, R M, Kristensen, P L, Beck-Nielsen, H et al. (2016) Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type 1 diabetes prone to severe hypoglycaemia: The HypoAna trial. Diabetes & metabolism 42(4): 249-55	- Comparator in study does not match that specified in protocol Different bolus insulins used in each arm of the trial
Alemayehu, Berhanu, Speiser, Jessica, Bloudek, Lisa et al. (2018) Costs associated with long-acting insulin analogues in patients with diabetes. The American journal of managed care 24(8specno): p265-sp272	- Health economics analysis
Almeida, Paulo H R F, Silva, Thales B C, de Assis Acurcio, Francisco et al. (2018) Quality of Life of Patients with Type 1 Diabetes Mellitus Using Insulin Analog Glargine Compared with NPH Insulin: A Systematic Review and Policy Implications. The patient 11(4): 377-389	- Systematic review used as source of primary studies
Ampudia-Blasco, F.J. (2020) Biosimilars and Novel Insulins. American Journal of Therapeutics 27(1): e52-e61	- Study does not contain a relevant intervention Systematic review focused on rapid acting insulin.
Ashwell, Simon G, Bradley, Clare, Stephens, James W et al. (2008) Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. Diabetes care 31(6): 1112-7	- Comparator in study does not match that specified in protocol Different bolus insulins are used in each arm
Bailey, T S, Pettus, J, Roussel, R et al. (2018) Morning administration of 0.4U/kg/day insulin glargine 300U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100U/mL in type 1 diabetes. Diabetes & metabolism 44(1): 15-21	- Study does not contain outcomes of interest Pharmacodynamic and pharmacokinetic outcomes
Banarer, S (2008) Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. Diabetes care 31(3): e16	- Not a relevant study design Response to Porcellati 2007 article
Battelino, T., Bosnyak, Z., Danne, T. et al. (2020) InRange: Comparison of the Second-Generation Basal Insulin Analogues Glargine 300 U/mL and Degludec 100 U/mL in Persons with Type 1 Diabetes Using Continuous Glucose Monitoring-Study Design. Diabetes Therapy 11(4): 1017-1027	- study protocol InRange protocol
Becker, Reinhard H A, Dahmen, Raphael, Bergmann, Karin et al. (2015) New insulin glargine 300 Units . mL-1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units . mL-1. Diabetes care 38(4): 637-43	- Study does not contain outcomes of interest Pharmacokinetic and pharmacodynamic outcomes

Study	Reason
Bergenstal, R M, Lunt, H, Franek, E et al. (2016) Randomized, double-blind clinical trial comparing basal insulin peglispro and insulin glargine, in combination with prandial insulin lispro, in patients with type 1 diabetes: IMAGINE 3. Diabetes, obesity & metabolism 18(11): 1081-1088	- Study does not contain a relevant intervention Peglispro - basal insulin that is no longer produced
Blevins, T.C., Barve, A., Raiter, Y. et al. (2020) Efficacy and safety of MYL-1501D versus insulin glargine in people with type 1 diabetes mellitus: Results of the INSTRIDE 3 phase 3 switch study. Diabetes, Obesity and Metabolism 22(3): 365-372	- Study does not contain a relevant intervention Compares the effects of switching between glargine and biosimilar
Blevins, TC, Barve, A, Raiter, Y et al. (2019) Efficacy and Safety of MYL-1501D Versus Insulin Glargine in Patients With Type 1 Diabetes Mellitus: results of the INSTRIDE 3 Phase 3 Switch Study. Diabetes, obesity & metabolism	- Duplicate reference
Bolli, G.B., Kerr, D., Thomas, R. et al. (2009) Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: A randomized open parallel multicenter study (Diabetes Care (2009) 32, (1170-1176)). Diabetes Care 32(10): 1944	- Not a relevant study design Article erratum
Bradley, Clare, Plowright, Rosalind, Stewart, John et al. (2007) The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ. Health and quality of life outcomes 5: 57	- Comparator in study does not match that specified in protocol Evaluating the DTSQc
Brock Jacobsen, I, Vind, B F, Korsholm, L et al. (2011) Counter-regulatory hormone responses to spontaneous hypoglycaemia during treatment with insulin Aspart or human soluble insulin: a double-blinded randomized cross-over study. Acta physiologica (Oxford, England) 202(3): 337-47	- Study does not contain a relevant intervention Effects of rapid-acting insulin
Brown, Meagan A, Davis, Courtney S, Fleming, Laurie W et al. (2016) The role of Toujeo R, insulin glargine U-300, in the treatment of diabetes mellitus. Journal of the American Association of Nurse Practitioners 28(9): 503-9	- Review article but not a systematic review
Brunton, Stephen A (2007) Nocturnal hypoglycemia: answering the challenge with long-acting insulin analogs. MedGenMed : Medscape general medicine 9(2): 38	- Review article but not a systematic review
Buse, John B, Carlson, Anders L, Komatsu, Mitsuhisa et al. (2018) Fast-acting insulin aspart versus insulin aspart in the setting of insulin degludec-treated type 1 diabetes: Efficacy and safety from a randomized double-blind trial. Diabetes, obesity & metabolism 20(12): 2885-2893	- Study does not contain a relevant intervention Effects of rapid-acting insulin
Cada, D.J.; Levien, T.; Baker, D.E. (2005) Insulin detemir. Hospital Pharmacy 40(12): 1062-1073	- Review article but not a systematic review
Caires de Souza, Ana Luisa, de Assis Acurcio, Francisco, Guerra Junior, Augusto Afonso et al. (2014) Insulin glargine in a Brazilian state: should the government disinvest? An assessment based on a systematic review. Applied health economics and health policy 12(1): 19-32	- Systematic review used as source of primary studies

Study	Reason
Cameron, Chris G and Bennett, Heather A (2009) Cost-effectiveness of insulin analogues for diabetes mellitus. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 180(4): 400-7	- Health economics analysis
Carroll, D.G. and Meade, L. (2013) Mixing insulin glargine with rapid-acting insulin: A review of the literature. Diabetes Spectrum 26(2): 112-117	- Review article but not a systematic review
Chacra, A R, Kipnes, M, Ilag, L L et al. (2010) Comparison of insulin lispro protamine suspension and insulin detemir in basal-bolus therapy in patients with Type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association 27(5): 563-9	- Comparator in study does not match that specified in protocol
Clissold, R. and Clissold, S. (2007) Insulin glargine in the management of diabetes mellitus: An evidence-based assessment of its clinical efficacy and economic value. Core Evidence 2(2): 89-110	- Systematic review used as source of primary studies
Crutchlow, Michael F, Palcza, John S, Mostoller, Kate M et al. (2018) Single-dose euglycaemic clamp studies demonstrating pharmacokinetic and pharmacodynamic similarity between MK-1293 insulin glargine and originator insulin glargine (Lantus) in subjects with type 1 diabetes and healthy subjects. Diabetes, obesity & metabolism 20(2): 400-408	- Study does not contain a relevant intervention Lusduna - no longer in production
Dailey, G and Lavernia, F (2015) A review of the safety and efficacy data for insulin glargine 300 units/ml, a new formulation of insulin glargine. Diabetes, obesity & metabolism 17(12): 1107-14	- Review article but not a systematic review Review of EDITION trials
Danne, T.; Heinemann, L.; Bolinder, J. (2020) New Insulins, Biosimilars, and Insulin Therapy. Diabetes Technology and Therapeutics 22(s1): 32-s46	- Review article but not a systematic review
Danne, Thomas; Heinemann, Lutz; Bolinder, Jan (2017) New Insulins, Biosimilars, and Insulin Therapy. Diabetes technology & therapeutics 19(s1): 42-s58	- Review article but not a systematic review
Danne, Thomas, Lupke, Kerstin, Walte, Kerstin et al. (2003) Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. Diabetes care 26(11): 3087-92	- Study does not contain outcomes of interest And compares children v adults
Davies, M, Sasaki, T, Gross, J L et al. (2016) Comparison of insulin degludec with insulin detemir in type 1 diabetes: a 1-year treat-to-target trial. Diabetes, obesity & metabolism 18(1): 96-9	- Not a peer-reviewed publication Summary of Davies 2014 article
Davis, M D, Beck, R W, Home, P D et al. (2007) Early retinopathy progression in four randomized trials comparing insulin glargine and NPH [corrected] insulin. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 115(4): 240-3	- Review article but not a systematic review
Dawoud, Dalia, Fenu, Elisabetta, Higgins, Bernard et al. (2017) Basal Insulin Regimens for Adults with Type 1 Diabetes Mellitus: A Cost-Utility Analysis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 20(10): 1279-1287	- Health economics analysis

Study	Reason
Dawoud, Dalia, O'Mahony, Rachel, Wonderling, David et al. (2018) Basal Insulin Regimens for Adults with Type 1 Diabetes Mellitus: A Systematic Review and Network Meta-Analysis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 21(2): 176-184	- Systematic review used as source of primary studies
Dejgaard, A, Lynggaard, H, Rastam, J et al. (2009) No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. Diabetologia 52(12): 2507-12	- Not a relevant study design Individual patient data meta-analysis.
DeVries, J H, Lindholm, A, Jacobsen, J L et al. (2003) A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with Type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association 20(4): 312-8	- Study does not contain a relevant intervention Compares the effects of rapid-acting insulins
Devries, J H; Nattrass, M; Pieber, T R (2007) Refining basal insulin therapy: what have we learned in the age of analogues?. Diabetes/metabolism research and reviews 23(6): 441-54	- Review article but not a systematic review
Diez-Fernandez, Ana, Cavero-Redondo, Ivan, Moreno-Fernandez, Jesus et al. (2019) Effectiveness of insulin glargine U-300 versus insulin glargine U-100 on nocturnal hypoglycemia and glycemic control in type 1 and type 2 diabetes: a systematic review and meta-analysis. Acta diabetologica 56(3): 355-364	- Systematic review used as source of primary studies
Dzygalo, K, Golicki, D, Kowalska, A et al. (2015) The beneficial effect of insulin degludec on nocturnal hypoglycaemia and insulin dose in type 1 diabetic patients: a systematic review and meta-analysis of randomised trials. Acta diabetologica 52(2): 231-8	- Systematic review used as source of primary studies
Einhorn, Daniel, Handelsman, Yehuda, Bode, Bruce W et al. (2015) PATIENTS ACHIEVING GOOD GLYCEMIC CONTROL (HBA1c <7%) EXPERIENCE A LOWER RATE OF HYPOGLYCEMIA WITH INSULIN DEGLUDEC THAN WITH INSULIN GLARGINE: A META-ANALYSIS OF PHASE 3A TRIALS. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 21(8): 917-26	- Systematic review used as source of primary studies
Ericsson, A., Pollock, R.F., Hunt, B. et al. (2013) Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. Journal of Medical Economics 16(12): 1442-1452	- Health economics analysis
Evans, M., Mehta, R., Gundgaard, J. et al. (2018) Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting. Diabetes Therapy 9(5): 1919-1930	- Health economics analysis
Feleder, E C, Yerino, G A, Halabe, E K et al. (2012) Phase IV study comparing diurnal glycemic profile following the administration of 2 NPH plus regular human DNA recombinant insulin regimens in type 1 diabetes mellitus (T1DM) adult patients. Arzneimittel-Forschung 62(6): 267-73	- Comparator in study does not match that specified in protocol Different rapid-acting insulins used in each treatment arm
Freemantle, N, Evans, M, Christensen, T et al. (2013) A comparison of health-related quality of life (health utility) between insulin degludec and insulin glargine: a meta-analysis of phase 3 trials. Diabetes, obesity & metabolism 15(6): 564-71	- Systematic review used as source of primary studies

Study	Reason
Frier, B M; Russell-Jones, D; Heise, T (2013) A comparison of insulin detemir and neutral protamine Hagedorn (isophane) insulin in the treatment of diabetes: a systematic review. Diabetes, obesity & metabolism 15(11): 978-86	- Systematic review used as source of primary studies
Gale, E A (2000) A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with Type 1 diabetes on intensified insulin therapy. The UK Trial Group. Diabetic medicine : a journal of the British Diabetic Association 17(3): 209-14	- Study does not contain a relevant intervention Rapid acting insulin. Type of basal insulin was not controlled
Garg, S.K., Wernicke-Panten, K., Rojeski, M. et al. (2017) Efficacy and Safety of Biosimilar. Diabetes Technology and Therapeutics 19(9): 516-526	- Review article but not a systematic review
Garg, S.K., Wernicke-Panten, K., Wardecki, M. et al. (2020) Safety, Immunogenicity and Glycemic Control of Insulin Aspart Biosimilar SAR341402 Versus Originator Insulin Aspart in People with Diabetes also Using Insulin Glargine: 12-Month Results from the GEMELLI 1 Trial. Diabetes technology & therapeutics	- Study does not contain the population of interest Includes people with Type 1 and Type 2 diabetes. Results not reported separately
Garg, S.K., Wernicke-Panten, K., Wardecki, M. et al. (2020) Efficacy and Safety of Insulin Aspart Biosimilar SAR341402 Versus Originator Insulin Aspart in People with Diabetes Treated for 26 Weeks with Multiple Daily Injections in Combination with Insulin Glargine: A Randomized Open-Label Trial (GEMELLI 1). Diabetes Technology and Therapeutics 22(2): 85-95	- Study does not contain a relevant intervention Effects of rapid-acting insulin and biosimilar
Garg, S, Dreyer, M, Jinnouchi, H et al. (2016) A randomized clinical trial comparing basal insulin peglispro and insulin glargine, in combination with prandial insulin lispro, in patients with type 1 diabetes: IMAGINE 1. Diabetes, obesity & metabolism 18suppl2: 25-33	- Study does not contain a relevant intervention Peglispro - basal insulin that is no longer produced
Garg, Satish K, Wernicke-Panten, Karin, Rojeski, Maria et al. (2017) Efficacy and Safety of Biosimilar SAR342434 Insulin Lispro in Adults with Type 1 Diabetes Also Using Insulin Glargine-SORELLA 1 Study. Diabetes technology & therapeutics 19(9): 516-526	- Study does not contain a relevant intervention Compares effects of rapid-acting insulin
Garg, Satish; Ampudia-Blasco, Francisco Javier; Pfohl, Martin (2010) Rapid-acting insulin analogues in Basal-bolus regimens in type 1 diabetes mellitus. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 16(3): 486-505	- Study does not contain a relevant intervention Systematic review focuses on rapid acting insulin
Garg, Satish, Moser, Emily, Dain, Marie-Paule et al. (2010) Clinical experience with insulin glargine in type 1 diabetes. Diabetes technology & therapeutics 12(11): 835-46	- Systematic review used as source of primary studies
Gerich, John, Becker, Reinhard H A, Zhu, Ray et al. (2006) Fluctuation of serum basal insulin levels following single and multiple dosing of insulin glargine. Diabetes technology & therapeutics 8(2): 237-43	- Review article but not a systematic review
Goldman, Jennifer and White, John R Jr (2015) New Insulin Glargine 300 U/mL for the Treatment of Type 1 and Type 2 Diabetes Mellitus. The Annals of pharmacotherapy 49(10): 1153-61	- Systematic review used as source of primary studies

Study	Reason
Goldman-Levine, Jennifer D; Patel, Dhiren K; Schnee, David M (2013) Insulin degludec: a novel basal insulin analogue. The Annals of pharmacotherapy 47(2): 269-77	- Review article but not a systematic review
Gough, Stephen C L (2007) A review of human and analogue insulin trials. Diabetes research and clinical practice 77(1): 1-15	- Study does not contain a relevant intervention Systematic review focused on rapid acting analogues insulin lispro and insulin aspart.
Gschwend, Manuela Helena; Aagren, Mark; Valentine, William J (2009) Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. Journal of medical economics 12(2): 114-23	- Health economics analysis
Guillermin, Anne-Laure, Samyshkin, Yevgeniy, Wright, Donna et al. (2011) Modeling the lifetime costs of insulin glargine and insulin detemir in type 1 and type 2 diabetes patients in Canada: a meta-analysis and a cost-minimization analysis. Journal of medical economics 14(2): 207-16	- Health economics analysis
Haahr, Hanne, Sasaki, Tomio, Bardtrum, Lars et al. (2016) Insulin degludec/insulin aspart in Japanese patients with type 1 diabetes mellitus: Distinct prandial and basal glucose-lowering effects. Journal of diabetes investigation 7(4): 574-80	- Study does not contain a relevant intervention Premixed intermediate and rapid acting insulin
Hagenmeyer EG, Schadlich PK, Koster AD, Dippel FW, Haussler B (2009) [Quality of life and treatment satisfaction in patients being treated with long-acting insulin analogues: systematic review]. Deutsche Medizinische Wochenschrift 134(12): 565-570	- Study not reported in English
Hagenmeyer, E.-G., Koltermann, K.C., Dippel, F.-W. et al. (2011) Health economic evaluations comparing insulin glargine with NPH insulin in patients with type 1 diabetes: A systematic review. Cost Effectiveness and Resource Allocation 9: 15	- Health economics analysis
Heise, Tim, Hovelmann, Ulrike, Nosek, Leszek et al. (2015) Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. Expert opinion on drug metabolism & toxicology 11(8): 1193-201	- Study does not contain outcomes of interest Compares different doses of insulin but reports AEs as a single result. Not clear what doses resulted in AEs
Heise, Tim, Nosek, Leszek, Ronn, Birgitte Biilmann et al. (2004) Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 53(6): 1614-20	- Study does not contain outcomes of interest Pharmacokinetic and pharmacodynamic outcomes
Heller, S R, Amiel, S A, Evans, M L et al. (2002) Does insulin lispro preserve the physiological defences to hypoglycaemia during intensive insulin therapy with a conventional basal bolus regimen?. Diabetes, obesity & metabolism 4(2): 106-12	- Study does not contain a relevant intervention Investigating effects of rapid-acting insulin
Heller, S, Mathieu, C, Kapur, R et al. (2016) A meta-analysis of rate ratios for nocturnal confirmed hypoglycaemia with insulin degludec vs. insulin glargine using different definitions for hypoglycaemia. Diabetic medicine : a journal of the British Diabetic Association 33(4): 478-87	- Systematic review used as source of primary studies

Study	Reason
Heller, Simon, Bode, Bruce, Kozlovski, Plamen et al. (2013) Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. Journal of diabetes 5(4): 482-91	- Study does not contain a relevant intervention Systematic review of rapid-acting insulin
Hemmingsen, B; Richter, B; Metzendorf, MI (2019) (Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus. Cochrane Database of Systematic Reviews	- study protocol
Hermansen, K, Fontaine, P, Kukolja, K K et al. (2004) Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 47(4): 622-9	- Comparator in study does not match that specified in protocol Different rapid-acting insulins used in combination with each long-acting insulin
Hermansen, Kjeld, Vaaler, Stein, Madsbad, Sten et al. (2002) Postprandial glycemic control with biphasic insulin aspart in patients with type 1 diabetes. Metabolism: clinical and experimental 51(7): 896-900	- Study does not contain a relevant intervention Compares rapid acting insulins
Hershon, Kenneth S, Blevins, Thomas C, Mayo, Christy A et al. (2004) Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 10(1): 10-7	- Secondary publication of an included study that does not provide any additional relevant information Subgroup analysis of Ratner 2000
Hirsch, I B, Franek, E, Mersebach, H et al. (2017) Safety and efficacy of insulin degludec/insulin aspart with bolus mealtime insulin aspart compared with standard basal-bolus treatment in people with Type 1 diabetes: 1-year results from a randomized clinical trial (BOOST R T1). Diabetic medicine : a journal of the British Diabetic Association 34(2): 167-173	- Study does not contain a relevant intervention Study included mixed insulin (Degludec + aspart)
Hirsch, Irl B, Bode, Bruce, Courreges, Jean-Pierre et al. (2012) Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal-bolus regimen in patients with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. Diabetes care 35(11): 2174-81	- Study does not contain a relevant intervention Study included mixed insulin (Degludec + aspart)
Holmes, R.S.; Crabtree, E.; McDonagh, M.S. (2019) Comparative effectiveness and harms of long-acting insulins for type 1 and type 2 diabetes: A systematic review and meta-analysis. Diabetes, Obesity and Metabolism 21(4): 984-992	- Systematic review used as source of primary studies
Home, P D and Lagarenne, P (2009) Combined randomised controlled trial experience of malignancies in studies using insulin glargine. Diabetologia 52(12): 2499-506	- Not a relevant study design
Hoogwerf, Byron J, Lincoff, A Michael, Rodriguez, Angel et al. (2016) Major adverse cardiovascular events with basal insulin peglispro versus comparator insulins in patients with type 1 or type 2 diabetes: a meta-analysis. Cardiovascular diabetology 15: 78	- Study does not contain a relevant intervention Systematic review for Peglispro - basal insulin that is no longer produced

Study	Reason
Jacober, S J, Rosenstock, J, Bergenstal, R M et al. (2014) Contrasting weight changes with LY2605541, a novel long-acting insulin, and insulin glargine despite similar improved glycaemic control in T1DM and T2DM. Diabetes, obesity & metabolism 16(4): 351-6	- Study does not contain a relevant intervention Peglispro - basal insulin that is no longer produced
Keating, Gillian M (2012) Insulin detemir: a review of its use in the management of diabetes mellitus. Drugs 72(17): 2255-87	- Systematic review used as source of primary studies
Koehler, G, Treiber, G, Wutte, A et al. (2014) Pharmacodynamics of the long-acting insulin analogues detemir and glargine following single-doses and under steady-state conditions in patients with type 1 diabetes. Diabetes, obesity & metabolism 16(1): 57-62	- Study does not contain a relevant intervention Bolus insulin not controlled
Koehler, Gerd, Heller, Simon, Korsatko, Stefan et al. (2014) Insulin degludec is not associated with a delayed or diminished response to hypoglycaemia compared with insulin glargine in type 1 diabetes: a double-blind randomised crossover study. Diabetologia 57(1): 40-9	- Study does not contain outcomes of interest
Komuro, Manaho, Inoue, Gaku, Tabata, Mitsuhisa et al. (2015) Insulin degludec requires lower bolus insulin doses than does insulin glargine in Japanese diabetic patients with insulin-dependent state. Journal of diabetes science and technology 9(3): 632-8	- Study does not contain a relevant intervention Bolus insulin not controlled
Korsatko, S, Deller, S, Mader, J K et al. (2014) Ultra-long pharmacokinetic properties of insulin degludec are comparable in elderly subjects and younger adults with type 1 diabetes mellitus. Drugs & aging 31(1): 47-53	- Comparator in study does not match that specified in protocol Compares elderly vs younger patients rather than types of insulin
Korsatko, S, Glettler, K, Olsen, K J et al. (2013) A direct comparison of the pharmacodynamic properties of insulin detemir and neutral protamine lispro insulin in patients with type 1 diabetes. Diabetes, obesity & metabolism 15(3): 241-5	- Study does not contain outcomes of interest
Korsatko, Stefan, Deller, Sigrid, Koehler, Gerd et al. (2013) A comparison of the steady-state pharmacokinetic and pharmacodynamic profiles of 100 and 200 U/mL formulations of ultra-long-acting insulin degludec. Clinical drug investigation 33(7): 515-21	- Study does not contain outcomes of interest
Kudva, Yogish C, Basu, Ananda, Jenkins, Gregory D et al. (2007) Glycemic variation and hypoglycemia in patients with well-controlled type 1 diabetes on a multiple daily insulin injection program with use of glargine and ultralente as basal insulin. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 13(3): 244-50	- Study does not contain outcomes of interest
Lajara, Rosemarie; Cengiz, Eda; Tanenberg, Robert J (2017) The role of the new basal insulin analogs in addressing unmet clinical needs in people with type 1 and type 2 diabetes. Current medical research and opinion 33(6): 1045-1055	- Systematic review used as source of primary studies

Study	Reason
Lamos, E.M., Younk, L.M., Tate, D.B. et al. (2016) Pharmacokinetics and pharmacodynamics of insulin glargine-insulin glulisine basal-bolus and twice-daily premixed analog insulin in type 1 diabetes mellitus patients during three standardized meals. Journal of Clinical and Translational Endocrinology 3: 14-20	- Comparator in study does not match that specified in protocol Different rapid-acting insulins used in each arm
Laranjeira, Fernanda O, de Andrade, Keitty R C, Figueiredo, Ana C M G et al. (2018) Long-acting insulin analogues for type 1 diabetes: An overview of systematic reviews and meta-analysis of randomized controlled trials. PloS one 13(4): e0194801	- Systematic review used as source of primary studies
Levien, Terri L, Baker, Danial E, White, John R Jr et al. (2002) Insulin glargine: a new basal insulin. The Annals of pharmacotherapy 36(6): 1019-27	- Review article but not a systematic review
Little, Stuart; Shaw, James; Home, Philip (2011) Hypoglycemia rates with basal insulin analogs. Diabetes technology & therapeutics 13suppl1: 53-64	- Systematic review used as source of primary studies
Liu, W.; Yang, X.; Huang, J. (2018) Efficacy and safety of insulin degludec versus insulin glargine: A systematic review and meta-analysis of fifteen clinical trials. International Journal of Endocrinology 2018: 8726046	- Systematic review used as source of primary studies
Ma, Zhulin, Christiansen, Jens Sandahl, Laursen, Torben et al. (2014) Short-term effects of NPH insulin, insulin detemir, and insulin glargine on the GH-IGF1-IGFBP axis in patients with type 1 diabetes. European journal of endocrinology 171(4): 471-9	- Study does not contain outcomes of interest
Marra, L.P., Araujo, V.E., Silva, T.B.C. et al. (2016) Clinical Effectiveness and Safety of Analog Glargine in Type 1 Diabetes: A Systematic Review and Meta-Analysis. Diabetes Therapy 7(2): 241-258	- Systematic review used as source of primary studies Systematic review included cohort studies.
Mathiesen, E.R., Hod, M., Ivanisevic, M. et al. (2014) Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Technology and Therapeutics 16(suppl1): 72-s73	- Wrong population Study includes pregnant woment with type 1 diabetes
Mathiesen, ER, Hod, M, Ivanisevic, M et al. (2014) Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes technology & therapeutics 16(suppl1): S72-S73	- Duplicate reference
Mathieu, Chantal, Bode, Bruce W, Franek, Edward et al. (2018) Efficacy and safety of fast-acting insulin aspart in comparison with insulin aspart in type 1 diabetes (onset 1): A 52-week, randomized, treat-to-target, phase III trial. Diabetes, obesity & metabolism 20(5): 1148-1155	- Study does not contain a relevant intervention Compares effects of rapid acting insulins
McEwan, P., Poole, C.D., Tetlow, T. et al. (2007) Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK. Current Medical Research and Opinion, Supplement 23(1): 7-s19	- Health economics analysis

Study	Reason
Miura, H., Sakaguchi, K., Okada, Y. et al. (2018) Effects of Insulin Degludec and Insulin Glargine U300 on Day-to-Day Fasting Plasma Glucose Variability in Individuals with Type 1 Diabetes: A Multicenter, Randomized, Crossover Study (Kobe Best Basal Insulin Study 2). Diabetes Therapy 9(6): 2399-2406	- study protocol
Monami, M; Marchionni, N; Mannucci, E (2009) Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis. Diabetes, obesity & metabolism 11(4): 372-8	- Systematic review used as source of primary studies
Monami, Matteo and Mannucci, Edoardo (2013) Efficacy and safety of degludec insulin: a meta-analysis of randomised trials. Current medical research and opinion 29(4): 339-42	- More recent systematic review included that covers the same topic
Morrow, L A, Hompesch, M, Jacober, S J et al. (2016) Glucodynamics of long-acting basal insulin peglispro compared with insulin glargine at steady state in patients with type 1 diabetes: substudy of a randomized crossover trial. Diabetes, obesity & metabolism 18(11): 1065-1071	- Comparator in study does not match that specified in protocol Study compared glargine and basal insulin peglispro.
Mullins, Peter, Sharplin, Peter, Yki-Jarvinen, Hannele et al. (2007) Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven Phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. Clinical therapeutics 29(8): 1607-19	- Not relevant to review question Meta-regression examining the interaction between hypglycaemia and HbA1c.
Nishiyama, H, Shingaki, T, Suzuki, Y et al. (2018) Similar Intrapatient Blood Glucose Variability with LY2963016 and Lantus Insulin Glargine in Patients with Type 1 (T1D) or Type 2 Diabetes, Including a Japanese T1D Subpopulation. Diabetes therapy 9(4): 1469-1476	- Study does not contain outcomes of interest Study evaluated the interpatient blood glucose variability. Study used data from ELEMENT 1 and ELEMENT 2 trial.
Ocheltree, S M, Hompesch, M, Wondmagegnehu, E T et al. (2010) Comparison of pharmacodynamic intrasubject variability of insulin lispro protamine suspension and insulin glargine in subjects with type 1 diabetes. European journal of endocrinology 163(2): 217-23	- Study does not contain a relevant intervention Study compared insulin lisrp protamine suspension within insulin glargine
Ono, Y., Nishida, T., Hyllested-Winge, J. et al. (2016) A comparison of IDeg + IAsp versus IDet + IAsp in subjects with type 1 diabetes: subgroup analysis of Japanese subjects. Diabetology International 7(4): 404-412	- Does not contain a population of people with XXX Post hoc analysis of Davies 2016 only focusing on Japanese population
Ooi Cheow Peng, Ting Tzer Hwu, Loke Seng Cheong (2014) Ultra-long acting insulin versus long-acting insulin for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews: Reviews issue5	- study protocol
Palmer, Andrew J, Roze, Stephane, Valentine, William J et al. (2004) Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Current medical research and opinion 20(11): 1729-46	- Health economics analysis

Study	Reason
Palmer, Andrew J, Valentine, William J, Ray, Joshua A et al. (2007) An economic assessment of analogue basal-bolus insulin versus human basal-bolus insulin in subjects with type 1 diabetes in the UK. Current medical research and opinion 23(4): 895-901	- Health economics analysis
Pedersen-Bjergaard, Ulrik, Kristensen, Peter Lommer, Beck-Nielsen, Henning et al. (2014) Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. The lancet. Diabetes & endocrinology 2(7): 553-61	- Study does not contain a relevant intervention Patients randomised to determir+aspart and human NPH+ human regular insulin.
Pesić, M, Zivić, S, Radenković, S et al. (2007) Comparison between basal insulin glargine and NPH insulin in patients with diabetes type 1 on conventional intensive insulin therapy. Vojnosanitetski pregled 64(4): 247-252	- Study not reported in English
Peterson, G.E. (2006) Intermediate and long-acting insulins: A review of NPH insulin, insulin glargine and insulin detemir. Current Medical Research and Opinion 22(12): 2613-2619	- Review article but not a systematic review
Philis-Tsimikas, A., Lane, W., Pedersen-Bjergaard, U. et al. (2020) The relationship between HbA1c and hypoglycaemia in patients with diabetes treated with insulin degludec versus insulin glargine 100 units/mL. Diabetes, Obesity and Metabolism 22(5): 779-787	- Study does not contain outcomes of interest Study investigated the association between individual patient risk of hypoglycaemia and HbA1c
Pieber, T R; Eugene-Jolchine, I; Derobert, E (2000) Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. Diabetes care 23(2): 157-62	- Duplicate reference
Plum, M.-B.F.; Sicat, B.L.; Brokaw, D.K. (2003) Newer Insulin Therapies for Management of Type 1 and Type 2 Diabetes Mellitus. Consultant Pharmacist 18(5): 454-465	- Full text paper not available
Polonsky, William, Traylor, Louise, Gao, Ling et al. (2017) Improved treatment satisfaction in patients with type 1 diabetes treated with insulin glargine 100U/mL versus neutral protamine Hagedorn insulin: An exploration of key predictors from two randomized controlled trials. Journal of diabetes and its complications 31(3): 562-568	- Not a relevant study design Retrospective, pooled patient-level analysis
Porcellati, F, Rossetti, P, Bolli, GB et al. (2008) Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. Diabetes care 31(3): e17	- Study does not contain outcomes of interest Study explored pharmacokinetics of long acting insulin analogs
Porcellati, Francesca, Lucidi, Paola, Candeloro, Paola et al. (2019) Pharmacokinetics, Pharmacodynamics, and Modulation of Hepatic Glucose Production With Insulin Glargine U300 and Glargine U100 at Steady State With Individualized Clinical Doses in Type 1 Diabetes. Diabetes care 42(1): 85-92	- Study does not contain outcomes of interest Study focused on pharmacokinetics and pharmacodynamics

Study	Reason
Porcellati, Francesca, Rossetti, Paolo, Busciantella, Natalia Ricci et al. (2007) Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. Diabetes care 30(10): 2447-52	- Study does not contain outcomes of interest Study focuses on pharmacokinetics
Ratner, R E, Gough, S C L, Mathieu, C et al. (2013) Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes, obesity & metabolism 15(2): 175-84	- Systematic review used as source of primary studies
Reutrakul, S.; Wroblewski, K.; Brown, R.L. (2012) Clinical use of U-500 regular insulin: Review and meta-analysis. Journal of Diabetes Science and Technology 6(2): 412-420	- Study does not contain a relevant intervention
Roach, P, Strack, T, Arora, V et al. (2001) Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin lispro protamine suspension in patients with types 1 and 2 diabetes. International journal of clinical practice 55(3): 177-82	- Full text paper not available
Rosak, C; Jung, R; Hofmann, U (2008) Insulin glargine maintains equivalent glycemic control and better lipometabolic control than NPH insulin in type 1 diabetes patients who missed a meal. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 40(8): 544-8	- Not relevant to review question Study investigated blood glucose and lipometabolism in patients who missed breakfast and their accompanying insulin injection.
Rosenstock, Julio, Bergenstal, Richard M, Blevins, Thomas C et al. (2013) Better glycemic control and weight loss with the novel long-acting basal insulin LY2605541 compared with insulin glargine in type 1 diabetes: a randomized, crossover study. Diabetes care 36(3): 522-8	- Study does not contain a relevant intervention Peglispro - basal insulin that is no longer produced
Rosenstock, Julio, Marre, Michel, Qu, Yongming et al. (2016) Reduced nocturnal hypoglycaemia with basal insulin peglispro compared with insulin glargine: pooled analyses of five randomized controlled trials. Diabetes, obesity & metabolism 18(11): 1093-1097	- Study does not contain a relevant intervention Systematic review of Peglispro - basal insulin that is no longer produced
Rosselli, J.L., Archer, S.N., Lindley, N.K. et al. (2015) U300 Insulin Glargine: A Novel Basal Insulin for Type 1 and Type 2 Diabetes. Journal of Pharmacy Technology 31(5): 234-242	- Systematic review used as source of primary studies
Russell-Jones, D, Gall, M-A, Niemeyer, M et al. (2015) Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials. Nutrition, metabolism, and cardiovascular diseases : NMCD 25(10): 898-905	- Systematic review used as source of primary studies
Saberi, S., Esfandiari, N.H., MacEachern, M.P. et al. (2015) Detemir plus aspart and glulisine induced lipoatrophy: 2015 literature review and report of a new case. Clinical Diabetes and Endocrinology 1(1): 10	- Not a relevant study design Systematic reviews of case studies
Sanches, Andreia Cristina Conegero, Correr, Cassyano Januario, Venson, Rafael et al. (2011) Revisiting the efficacy of long-acting insulin analogues on adults with type 1 diabetes using mixed-treatment comparisons. Diabetes research and clinical practice 94(3): 333-9	- Systematic review used as source of primary studies

Study	Reason
Saunders, Sheena B (2009) Intermediate-acting vs. long-acting insulin for type 1 diabetes mellitus. Journal of Advanced Nursing 65(6): 1182-1183	- Not a relevant study design Review of a summary
Shafie, Asrul Akmal, Ng, Chin Hui, Tan, Yui Ping et al. (2017) Systematic Review of the Cost Effectiveness of Insulin Analogues in Type 1 and Type 2 Diabetes Mellitus. PharmacoEconomics 35(2): 141-162	- Health economics analysis Systematic review of cost effectiveness.
Shiramoto, M, Eto, T, Irie, S et al. (2015) Single-dose new insulin glargine 300 U/ml provides prolonged, stable glycaemic control in Japanese and European people with type 1 diabetes. Diabetes, obesity & metabolism 17(3): 254-60	- Study does not contain outcomes of interest
Siegmund, Thorsten, Tentolouris, Nikolaos, Knudsen, Soren T et al. (2018) A European, multicentre, retrospective, non-interventional study (EU-TREAT) of the effectiveness of insulin degludec after switching basal insulin in a population with type 1 or type 2 diabetes. Diabetes, obesity & metabolism 20(3): 689-697	- Not a relevant study design Retrospective chart review
Silva, T.B.C., Almeida, P.H.R.F., Araujo, V.E. et al. (2018) Effectiveness and safety of insulin glargine versus detemir analysis in patients with type 1 diabetes: systematic review and meta-analysis. Therapeutic Advances in Endocrinology and Metabolism 9(8): 241-254	- Systematic review used as source of primary studies
Singh, Sumeet R, Ahmad, Fida, Lal, Avtar et al. (2009) Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 180(4): 385-97	- Systematic review used as source of primary studies
Smeeton, F, Shojaee Moradie, F, Jones, R H et al. (2009) Differential effects of insulin detemir and neutral protamine Hagedorn (NPH) insulin on hepatic glucose production and peripheral glucose uptake during hypoglycaemia in type 1 diabetes. Diabetologia 52(11): 2317-23	- Study does not contain outcomes of interest
Sorli, Christopher, Warren, Mark, Oyer, David et al. (2013) Elderly patients with diabetes experience a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine: a meta-analysis of phase IIIa trials. Drugs & aging 30(12): 1009-18	- Systematic review used as source of primary studies
Stades, Aline M E, Hoekstra, Joost B L, van den Tweel, Ingeborg et al. (2002) Additional lunchtime basal insulin during insulin lispro intensive therapy in a randomized, multicenter, crossover study in adults : a real-life design. Diabetes care 25(4): 712-7	- Not relevant to review question Study evaluated whether an additional dose of NPH at lunchtime might overcome insulinemia.
Steinstraesser, A, Schmidt, R, Bergmann, K et al. (2014) Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. Diabetes, obesity & metabolism 16(9): 873-6	- Not relevant to review question Study compared metabolism and metabolite pharmacokinetics of glargine U300 and glargine U100
Szypowska A, Golicki D, Groele L, Pankowska E (2011) Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. Polskie Archiwum Medycyny Wewnetrznej 121(7-8): 237-246	- Systematic review abstract

Study	Reason
Szypowska, Agnieszka, Golicki, Dominik, Groele, Lidia et al. (2011) Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. Polskie Archiwum Medycyny Wewnetrznej 121(78): 237-46	- Systematic review used as source of primary studies
Tang, Xulei, Yang, Lin, He, Zhiyu et al. (2012) Insulin glargine and cancer risk in patients with diabetes: a meta-analysis. PloS one 7(12): e51814	- Systematic review used as source of primary studies
Tentolouris, A; Eleftheriadou, I; Tentolouris, N (2018) Insulin degludec U100 is associated with lower risk for severe and symptomatic hypoglycemia as compared with insulin glargine U100 in subjects with type 1 diabetes. Annals of translational medicine 6(3)	- Review article but not a systematic review
Testa, Marcia A, Gill, Jasvinder, Su, Max et al. (2012) Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. The Journal of clinical endocrinology and metabolism 97(10): 3504-14	- Comparator in study does not match that specified in protocol Patients were randomised to glargine-glulisine or premix analogue insulin (Humalog or Novolog).
Tieu, Carolyn, Lucas, Eleanor J, DePaola, Mindi et al. (2018) Efficacy and safety of biosimilar insulins compared to their reference products: A systematic review. PloS one 13(4): e0195012	- Systematic review used as source of primary studies
Tran K, Banerjee S, Li H, Cimon K, Daneman D, Simpson S H, Campbell K (2007) Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness.: 48	- Health economics analysis Systematic review used as a source of primary studies.
Tricco, Andrea C, Ashoor, Huda M, Antony, Jesmin et al. (2014) Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ (Clinical research ed.) 349: g5459	- Systematic review used as source of primary studies
Tunbridge, F K, Newens, A, Home, P D et al. (1989) Double-blind crossover trial of isophane (NPH)- and lente-based insulin regimens. Diabetes care 12(2): 115-9	- Study does not contain a relevant intervention Study compared NPH and lente based insulin regimens
Valentine, William J, Aagren, Mark, Haglund, Mattias et al. (2011) Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden. Scandinavian journal of public health 39(1): 79-87	- Health economics analysis
Valentine, William J, Palmer, Andrew J, Erny-Albrecht, Katrina M et al. (2006) Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH. Advances in therapy 23(2): 191-207	- Health economics analysis
van Golen, Larissa W, Veltman, Dick J, IJzerman, Richard G et al. (2014) Effects of insulin detemir and NPH insulin on body weight and appetite-regulating brain regions in human type 1 diabetes: a randomized controlled trial. PloS one 9(4): e94483	- Not relevant to review question

Study	Reason
	Study investigated whether detemir deferentially modifies brain activation in response to food stimuli as compared to NPH.
Vardi Moshe, Jacobson Eyal, Nini Asaph, Bitterman Haim (2008) Intermediate acting versus long acting insulin for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews: Reviews issue3	- Systematic review used as source of primary studies
Velussi, M, Cernigoi, A, Puglisi, C et al. (1989) Experimental study of the different potencies of biosynthetic and semisynthetic human insulin mixtures in the treatment of insulin-dependent diabetics. Curr ther res, clin exp 46(2): 390-398	- Full text paper not available
Vignati, L; Anderson, J H Jr; Iversen, P W (1997) Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. Clinical therapeutics 19(6): 1408-21	- Study does not contain a relevant intervention Study included lispro (rapid acting insulin)
Vora, J., Christensen, T., Rana, A. et al. (2014) Insulin Degludec Versus Insulin Glargine in Type 1 and Type 2 Diabetes Mellitus: A Meta-Analysis of Endpoints in Phase 3a Trials. Diabetes Therapy 5(2): 435-446	- Systematic review used as source of primary studies
Waldhausl, W., Howorka, K., Damjancic, P. et al. (1989) Human proinsulin for basal insulin replacement in IDDM. Diabetes, Nutrition and Metabolism - Clinical and Experimental 2(1): 25-31	- Full text paper not available
Wang, F.; Surh, J.; Kaur, M. (2012) Insulin degludec as an ultralong-acting basal insulin once a day: A systematic review. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 5: 191-204	- Systematic review used as source of primary studies
Wang, Fei; Carabino, Jana M; Vergara, Cunegundo M (2003) Insulin glargine: a systematic review of a long-acting insulin analogue. Clinical therapeutics 25(6): 1541-40	- Systematic review used as source of primary studies
Warren, E, Weatherley-Jones, E, Chilcott, J et al. (2004) Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health technology assessment (Winchester, England) 8(45): iii-57	- Health economics analysis
Woo, Vincent C (2017) A Review of the Clinical Efficacy and Safety of Insulin Degludec and Glargine 300 U/mL in the Treatment of Diabetes Mellitus. Clinical therapeutics 39(8s2): 12-s33	- Systematic review used as source of primary studies
Yamada, T., Kamata, R., Ishinohachi, K. et al. (2018) Biosimilar vs originator insulins: Systematic review and meta-analysis. Diabetes, Obesity and Metabolism 20(7): 1787-1792	- Systematic review used as source of primary studies
Zhang, Xiao-Wen, Zhang, Xin-Lin, Xu, Biao et al. (2018) Comparative safety and efficacy of insulin degludec with insulin glargine in type 2 and type 1 diabetes: a meta-analysis of randomized controlled trials. Acta diabetologica 55(5): 429-441	- Systematic review used as source of primary studies

Health economics

References of studies excluded after scanning by full text	Reason
All Wales Medicines Strategy Group (AWMSG). Insulin glargine (Abasaglar??). Penarth All Wales Ther Toxicol Cent (AWTTC), Secr All Wales Med Strateg Gr. Published online 2015. http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32015001232	Not a cost-utility analysis
Bottomley JM, Raymond FD. Pharmaco-economic issues for diabetes therapy. Insulin. 2009;4(1):32-60. doi:10.1016/s1557-0843%2809%2980005-5	Systematic Review
Brixner DI, McAdam-Marx C. Cost-effectiveness of insulin analogs. Am J Manag Care. 2008;14(11):766-775. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=352743073	Narrative Review
Dixon S, Peters JR. Evaluating the “real” cost-effectiveness of health technology: Reconciling the public interest with patients’ interests. Curr Med Res Opin Suppl. 2007;23(1):1-s6. doi:10.1185/030079907x167552	Narrative Review
Grunberger G. Insulin analogsdare they worth it. Diabetes Care. 2014;37(6):1767-1770. doi:10.2337/dc14-0031	Narrative Review
Hagenmeyer E-G, Koltermann KC, Dippel F-W, Schadlich PK. Health economic evaluations comparing insulin glargine with NPH insulin in patients with type 1 diabetes: A systematic review. Cost Eff Resour Alloc. 2011;9:15. doi:10.1186/1478-7547-9-15	Systematic Review
Holden SE, Currie CJ. Do the benefits of analog insulins justify their costs? Diabetes Manag. 2012;2(3):173-175. doi:10.2217/dmt.12.17	Narrative Review
Home P, Baik SH, Galvez GG, Malek R, Nikolajsen A. An analysis of the cost-effectiveness of starting insulin detemir in insulin-naive people with type 2 diabetes. J Med Econ. 2015;18(3):230-240. doi:10.3111/13696998.2014.985788	Inappropriate population - Gestational Diabetes/ Full text not available
Lee T-Y, Kuo S, Yang C-Y, Ou H-T. Cost-effectiveness of long-acting insulin analogues vs intermediate/long-acting human insulin for type 1 diabetes: A population-based cohort followed over 10 years. Br J Clin Pharmacol. 2020;86(5):852-860. doi:10.1111/bcp.14188	Not a cost-utility analysis
Nathan DM. Diabetes: Long-acting insulin analogues - Are benefits worth the cost? Nat Rev Endocrinol. 2012;8(12):699-700. doi:10.1038/nrendo.2012.208	Narrative Review
Pratoomsoot C, Smith HT, Kalsekar A, Boye KS, Arellano J, Valentine WJ. An estimation of the long-term clinical and economic benefits of insulin lispro in Type 1 diabetes in the UK. Diabet Med. 2009;26(8):803-814. doi:10.1111/j.1464-5491.2009.02775.x	Included in NG17 but excluded here due to insulin Lispro being a short acting insulin
Rubio Terres C Bolinder B, de Pablos P RJ. Cost-utility analysis of diabetes mellitus treatment with glargine insulin or NPH insulin in Spain. Rev Esp Econ la Salud. 2003;2(6):313-324. http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=22003001595	Not available in English
Shafie AA, Ng CH, Tan YP, Chaiyakunapruk N. Systematic Review of the Cost Effectiveness of Insulin Analogues in Type 1 and Type 2 Diabetes Mellitus. Pharmacoeconomics. 2017;35(2):141-162. doi:10.1007/s40273-016-0456-2	Systematic Review
Standl E, Owen DR. New long-acting basal insulins: Does benefit outweigh cost? Diabetes Care. 2016;39(supplement2):172-s179. doi:10.2337/dcs15-3011	Narrative Review

References of studies excluded after scanning by full text	Reason
Suh D-C, Aagren M. Cost-effectiveness of insulin detemir: a systematic review. Expert Rev Pharmacoecon Outcomes Res. 2011;11(6):641-655. doi:10.1586/erp.11.73	Systematic Review
Todorova-Ananieva K. Pharmacoeconomic analysis for the future treatment of diabetes mellitus after gestational diabetes. Acta Medica Bulg. 2010;37(1):39-50. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=360023384	Inappropriate population - Type 2 Diabetes
Tran K Li H, Cimon K, Daneman D, Simpson SH, Campbell K BS. Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of costeffectiveness. Ottawa Can Agency Drugs Technol Heal. Published online 2007:62isb1897465141. http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32007000623	Systematic Review
Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ. 2014;349:g5459. doi:10.1136/bmj.g5459	Systematic Review

Appendix P - Research recommendations – full details

None