Executive Summary

This submission presents evidence for the use of the Cypher sirolimus-eluting stent in the prevention of restenosis following PCI. Cordis re-affirm the data submitted during the previous appraisal that led to the publication of Guidance 71 and provide further longer term follow up data in support of the cost-effectiveness of Cypher in lesions longer than 15mm, vessels of <3mm in diameter and other higher-risk sub-groups.

Addressing Guidance 71 *recommendations for further research*, our submission contains longer-term follow-up data from the key Cypher trials; head to head results for Cypher compared with Taxus; and further evidence on the clinical and cost-effectiveness in diabetic patients.

Technological Improvements in the Cypher Sirolimus-eluting Stent

- The design of the Cypher stent has been changed since Guidance 71. The device marketed in the UK is now known as Cypher Select™ Sirolimus-eluting Coronary Stent.
- **Rationale**: The stent metal, drug, drug concentration, polymer and drug elution profile all remain unchanged. The stent architecture and delivery system in use during the procedure have been improved to aid deliverability.
- **Validation:** The randomised controlled DOMINO trial demonstrated non-inferiority of Cypher Select versus Cypher. The primary endpoint of the study was angiographic in-stent late loss at 6-month follow-up as determined by Quantitative Coronary Angiography.
- **Results:** Table E1 shows the key angiographic and intravascular ultrasound (IVUS) outcomes at 6m follow up. The primary endpoint of late loss was not significantly different between the two groups.

Table E1	**Cypher Select**	**Cypher**	**P**
Late loss (mm)	0.07 ± 0.35	0.13 ± 0.28	0.46
In-stent restenosis	1.8% (1/55)	0.0% (0/36)	1.00
Aneurysm at follow-up	0.0% (0/55)	0.0% (0/36)	-
Volume obstruction within stent (%)	3.15 ± 4.87	3.25 ± 4.89	0.95

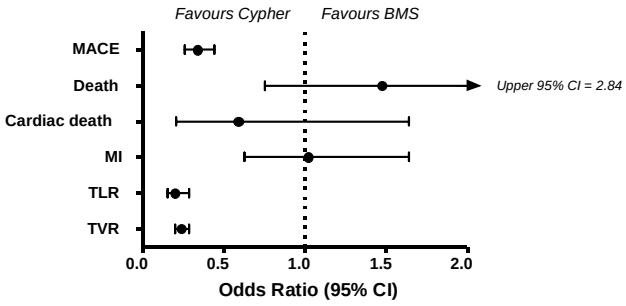
- **Conclusion:** The introduction of Cypher Select means that lesions that were previously too difficult to access with the original Cypher design can now be reached and treated effectively. The DOMINO trial demonstrates that there are no clinical differences between Cypher and Cypher Select, and therefore the clinical evidence related to Cypher should be considered appropriate for Cypher Select.

Comparison of Drug Eluting Stents

- The drug, the stent and the drug elution profile are all important components of a drug-eluting stent that contribute to the overall clinical effectiveness.
- Different drugs (e.g sirolimus and paclitaxel) act by very different mechanisms and have different therapeutic windows. It is therefore important that DES are not by default treated as an identical class of devices.
- Devices employing the same drug, but a different elution profile can have different outcomes, demonstrated by the DELIVER trial (Lansky et al, 2004).
- There have been attempts to develop lower cost devices by taking short cuts such as spraying the drug directly onto the stent. This approach is unlikely to be successful because it lacks the element of controlled release over the period of time over which the restenosis process is most active.

Clinical Effectiveness of Cypher

- 2 year follow-up data for the 4 key Cypher vs BMS trials report no significant difference in the safety endpoints of death, cardiac death or myocardial infarction between Cypher and the control bare metal stents (Figure E1).
- Clinically-driven target lesion revascularisation (TLR) and target lesion revascularisation (TVR) both remain significantly lower in the Cypher group, indicating that the benefit seen at 9 months (i.e. the data available at the time of the original Appraisal) is maintained to 2 years.



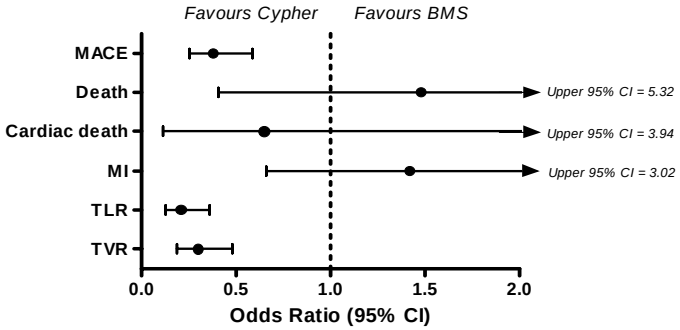
	Cypher			BMS			
720d Events	n	N	%	n	N	%	P
MACE	88	878	10.0%	215	870	24.7%	<0.0001
Death	22	878	2.5%	15	870	1.7%	0.32
Cardiac death	6	878	0.7%	10	870	1.1%	0.33
MI	36	878	4.1%	35	870	4.0%	1.00
TLR	46	878	5.2%	186	870	21.4%	<0.0001
TVR	61	878	6.9%	202	870	23.2%	<0.0001

Figure E1: 2-year meta-analysis of 4 Cypher RCTs

Sub Group Evaluations

Long lesions

The 2-year outcomes in long lesions (>15mm) support the effectiveness reported in the current guidance (Figure E2). These results are supported by an independent registry study, (Park, 2004).

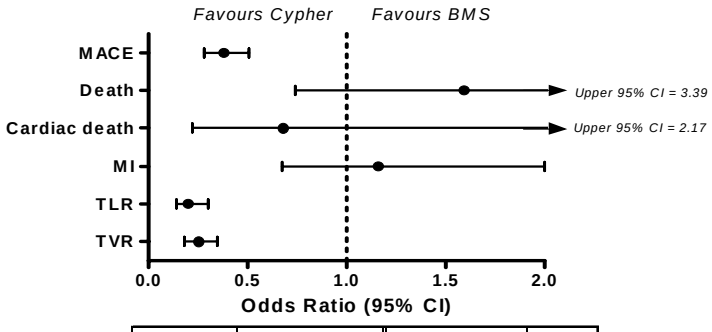


	Cypher			BMS			
720d Events	n	N	%	n	N	%	P
MACE	37	285	13.0%	79	280	28.2%	**<0.0001**
Death	6	285	2.1%	4	280	1.4%	**0.75**
Cardiac death	2	285	0.7%	3	280	1.1%	**0.68**
MI	17	285	6.0%	12	280	4.3%	**0.45**
TLR	21	285	7.4%	76	280	27.1%	**<0.0001**
TVR	30	285	10.5%	78	280	27.9%	**<0.0001**

Figure E2: 2-year outcomes, lesions >15mm

Small Vessels

2 year outcomes in small vessels (<3mm) support the effectiveness reported in the current guidance (Figure E3). These results are supported by another independent study (Ardissino *et al*, 2004).



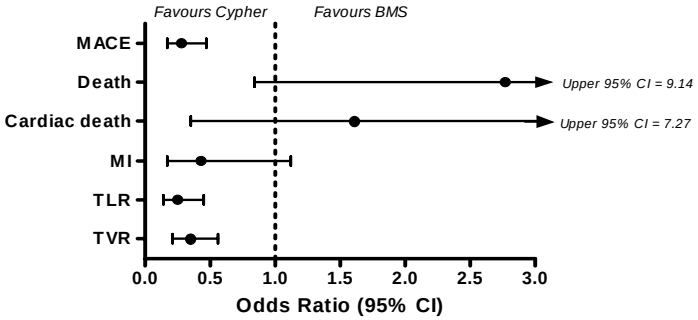
	Cypher			BMS			
720d Events	n	N	%	n	N	%	P
MACE	73	654	11.2%	157	628	25.0%	**<0.0001**
Death	18	654	2.8%	11	628	1.8%	**0.26**
Cardiac death	5	654	0.8%	7	628	1.1%	**0.57**
MI	30	654	4.6%	25	628	4.0%	**0.68**
TLR	36	654	5.5%	139	628	22.1%	**<0.0001**
TVR	54	654	8.3%	165	628	26.3%	**<0.0001**

Figure E3: 2-year outcomes, vessels <3mm

Diabetic Patients

- Numerous studies have shown that diabetes is an independent risk factor for restenosis and repeat revascularisation after stent placement (Kastrati *et al*, 1997; Singh *et al*, 2005; Iakovou *et al*, 2003; Kornowski *et al*, 1999).
- Diabetes was not identified as an independent risk factor by Bagust *et al* (2005), but the findings in this paper conflicted with other reported studies, including the 11,484-patient PRESTO trial (Singh *et al*, 2005).
- A review of diabetic patients within the Cypher clinical trials demonstrates the overall odds ratio for target vessel revascularisation at 2 years was 0.35 (95% CI 0.21 to 0.56) (Figure E4).

These results are also supported by the independent study, the DIABETES trial (Sabaté *et al*, 2004).



	Cypher			BMS			
720d Events	n	N	%	n	N	%	P
MACE	23	195	11.8%	75	233	32.2%	**<0.0001**
Death	9	195	4.6%	4	233	1.7%	**0.10**
Cardiac death	4	195	2.1%	3	233	1.3%	**0.71**
MI	6	195	3.1%	16	233	6.9%	**0.08**
TLR	16	195	8.2%	61	233	26.2%	**<0.0001**
TVR	27	195	13.8%	74	233	31.8%	**<0.0001**

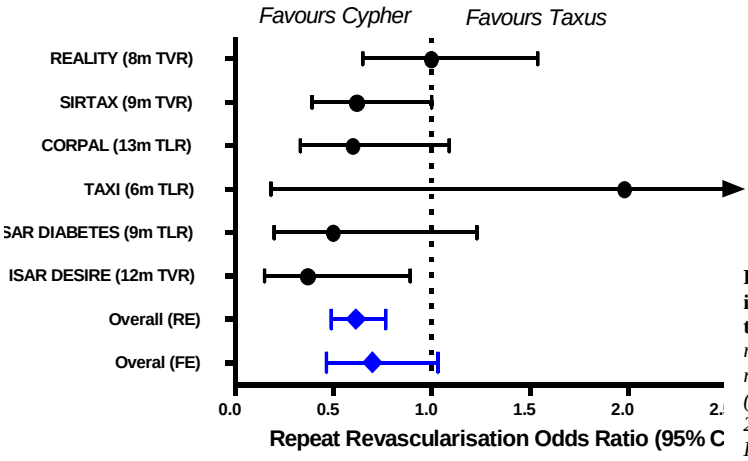
Figure E4: 2-year outcomes, diabetic

Implications of Diabetic results

- Of the 428 patients in the combined diabetic dataset, 51 (11.9%) would not 'qualify' for a DES according to current guidance.
- The BMS arm of this group had a 720-day target vessel revascularisation rate of 16.7% (5/30 patients).
- Assuming a minimum of 53,261 PCI procedures are performed in the UK per year (Ludman, 2004) and approximately 18% of those will be in diabetic patients (EUROASPIRE II Study Group, 2001), 9,587 diabetic patients will undergo PCI.
- If the guidance was extended to cover all diabetics, an additional 1,141 diabetic patients could benefit from receiving a DES instead of being put at 16.7% risk of TVR.

Cypher vs Taxus: Head-to-Head Comparison

- Available data permitted a head to head comparison of Cypher vs Taxus.
- Pooling results from 6 head to head studies provides enough statistical power (80%) to show a difference between the two devices.
- These results strongly suggest that Cypher confers a lower repeat revascularisation rate than Taxus.



	Cypher			Taxus			
Repeat Revascularisation	n	N	%	n	N	%	P
REALITY (8m TVR)	45	684	6.6%	44	669	6.6%	1.00
SIRTAX (9m TVR)	30	503	6.0%	47	509	9.2%	0.06
CORPAL (13m TLR)	19	434	4.4%	29	410	7.1%	0.10
TAXI (6m TLR)	2	102	2.0%	1	100	1.0%	1.00
ISAR DIABETES (9m TLR)	8	125	6.4%	15	125	12.0%	0.19
ISAR DESIRE (12m TVR)	8	100	8.0%	19	100	19.0%	0.04
Overall	**112**	**1948**	**5.8%**	**155**	**1913**	**8.1%**	

Figure E5: Odds ratios (95% confidence intervals) for repeat revascularisation in patients treated with either Cypher or Taxus. *RE = overall result using a random effects model. FE = overall result using a fixed effects model. The weight (1/variance) associated with each study is REALITY 20.78, SIRTAX 21.88, CORPAL 14.26, TAXI 0.50, ISAR DIABETES 7.02, ISAR DESIRE 8.74.*

Multivessel Disease

- The ARTS II trial was a single-arm study of patients with multivessel disease.
- 12-month results report a repeat revascularisation rate of 7.4%, similar to results for DES in single vessel disease trials.

In-Stent Restenosis

- Cypher is the only drug-eluting stent available in the UK market which is CE marked for the treatment of in-stent restenosis.
- The (non-J&J) ISAR-DESIRE trial demonstrates that Cypher is effective in this group.
- 300 patients with in-stent restenosis were randomised to balloon angioplasty, Cypher, or the Taxus paclitaxel-eluting stent. Approximately 30% of the patients were diabetic, vessel diameter was approximately 2.6mm and lesion length was approximately 12mm.
- At 1-year follow-up, both DES significantly reduced target vessel revascularisation versus balloon angioplasty (Cypher = 8.0%, Taxus = 19.0%, balloon = 33.0%).
- Registry data supports the evidence from the ISAR-DESIRE trial, and events are similar to those for other, *de novo* lesions (see 'Cypher in Routine Clinical Practice).

Safety and Experience from Routine Clinical Practice

- A review of 10 RCTs found that the incidence of total stent thrombosis or late thrombosis was no higher with DES than with BMS (Moreno *et al*, 2005).
- The safety and efficacy of Cypher has also been confirmed in the eCypher registry, an international registry of 15,566 patients treated with Cypher in routine clinical practice.

Cost Effectiveness

- The economic analysis submitted is a probabilistic model based on the combined data set reported in the clinical effectiveness section.
- A two-way analysis of Cypher v BMS is presented using the available 2-year data.
- A three-way analysis of Cypher v BMS v Taxus is presented using the available 1-year data.
- The evaluations are based on clinically-driven (*not angiographic*), target vessel (*not target lesion*) revascularisation where evidence permits.

Cost Effectiveness: Cypher v BMS

- The economic evaluation based on a 2 year model using patient-level data demonstrates Cypher would be cost effective compared to bare metal stents in patients with vessels <3mm in diameter, lesions >15mm length, or with diabetes, if the NHS is willing to pay up to £16,500 per QALY gained (Figure E6, Table E2).

Figure E6:

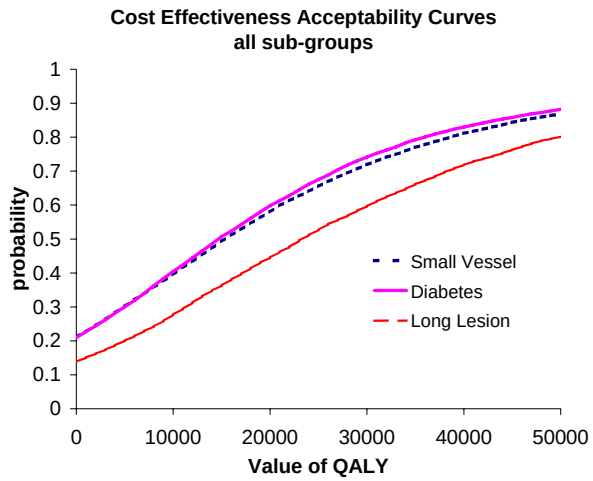


Table E2	
Scenario	**ICER**
No risk factors	£29,259
Small vessels	£10,178
Long lesions	£16,460
Diabetics	£9,702

Cost Effectiveness: Cypher v BMS v Taxus

- In the three-way analysis, comparing Cypher with BMS and Taxus, Cypher is still the most cost-effective option in all sub-groups of patients (long lesions, small vessels, and diabetic patients, Figures E7, E8, E9, Table E3) if the NHS is willing to pay up to £21,200 per QALY gained.

	Scenario	Mean QALYs	Mean Cost	ICER
No risk factors	BMS	-0.01186	*£1,760*	
	Taxus	-0.00469	£2,025	Extended Dominance
	Cypher	**-0.00353**	£2,044	£34,066
Small vessels	BMS	-0.01761	*£2079*	
	Taxus	-0.00753	£2199	Extended Dominance
	Cypher	**-0.00606**	£2214	£11,736
Long Lesions	BMS	-0.01469	*£1915*	
	Taxus	-0.00607	£2109	Extended Dominance
	Cypher	**-0.00475**	£2126	£21,177
Diabetics	BMS	-0.01733	*£1979*	
	Cypher	**-0.00532**	£2122	£11,925
	Taxus	-0.00707	£2123	Dominated

Table E3: ***Small vessels = vessels <3mm in diameter, long lesions = lesions >15mm length. ICER = incremental cost-effectiveness ratio. Stents are ranked by cost for each sub-group. The most effective option is highlighted in bold. The lowest cost option is highlighted in italic.***

Figure E7: Small Vessels

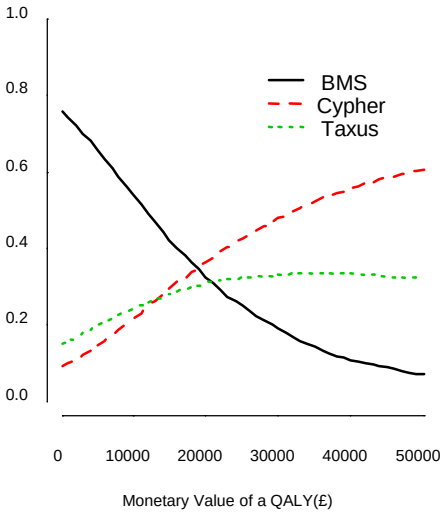


Figure E8: Long Lesions

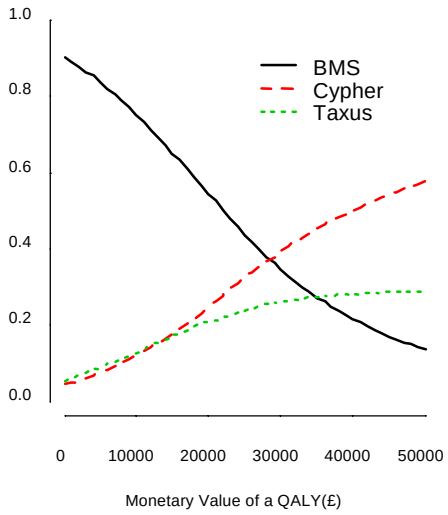


Figure E9: Diabetes