Belzutifan for treating tumours associated with Von Hippel-Lindau disease [ID3932]

For screen- redacted

Technology appraisal committee B

Chair: Charles Crawley

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Company: MSD

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Belzutifan for treating tumours associated with Von Hippel-Lindau disease

- ✓ **Key issues and background**
- ❑ Decision problem
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Key issues

Key issues for committee discussion	
Decision problem	• At what position would treatment with Belzutifan be initiated? • How long people would stay on the treatment? • Is the MK-6482-004 trial population reflective of DP population?
Clinical evidence	• What does disease control rate mean in MK-6284-004 vs. DP population?
	• Is the company approach to adjusting treatment effect appropriate?
Cost effectiveness	• How plausible are the model outputs?
	• Is the company's approach to implement ToT and treatment effect wanning appropriate?
	• Is it appropriate to assume an immediate HRQoL benefit for Belzutifan? Are the disutilities applied appropriate?
	• What is the appropriate severity modifier for Belzutifan?

Abbreviations; DP, decision problem; HRQoL, health-related quality of life; ToT, time on treatment

Background: Von Hippel-Lindau disease

Genetic disorder characterised by tumours & abnormal growth in multiple organs

Causes

- Defects in VHL gene responsible for production of a protein (pVHL) that regulates cell growth
- pVHL is critical for regulation of hypoxia-inducible factor (HIF) and loss of pVHL function that results in oncogenic stimulation and leads to growth of cysts and tumours in multiple organs

Epidemiology

- Prevalence between ~1 in 68,000 to 91,000 in England with 842 people in the UK
- 80% people inherit while 20% develop de novo VHL mutation
- Major tumour types include RCC , CNS haemangioblastomas & pNET (focus of this topic)

Symptoms and prognosis

- People develop a wide constellation of symptoms related to varying locations and types of tumours
- Symptoms also depend on size and location of tumours with eyes, cerebellum, spinal cord, kidneys, adrenal glands and pancreas frequently affected
- Early diagnosis and treatment may affect prognosis positively; high risk individuals undergo multidisciplinary surveillance

Abbreviations: CNS, central nervous system; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

Patient perspectives

Submissions from Action Kidney Cancer and VHL UK/Ireland

"I will gladly trade the fatigue and headaches for keeping my pancreas"

Living with VHL

- Rare, inherited, incurable disorder which causes tumours and cysts to grow in kidney, brain, spinal cord, eyes, inner ear, adrenal glands, pancreas, and reproductive system
- People suffer constant pain, headaches, confusion, paralysis, kidney disfunction, difficulties with daily living and regularly needing periods of rest during the day
- People have multiple interruptions in education, missed career opportunities, multiple surgeries and affects relationships

Unmet need

- Significant unmet need for an effective treatment for hereditary subtypes of kidney cancer, such as RCC caused by VHL disease which are difficult to treat
- Limited treatment options: people feel depressed, fear surgery, and low self-worth

"My son experiences great reduction of tumour in the brain, as well as reduction and stabilization of kidney cancer after taking Belzutifan"

Belzutifan

- First-in-class HIF inhibitor for treatment of VHL, innovative drug which could extend life expectancy of people VHL and significantly improve quality of life
- Will limit the need of multiple surgeries and reduction in number of people having dialysis
- Most side-effects are tolerable and manageable: compared to surgery people are willing to take risk

Abbreviations: HIF, hypoxia-inducible factor; VHL, Von Hippel-Lindau; RCC, renal cell carcinoma

Clinical perspectives

Submission from University of Cambridge

Aim of treatment

- Main aims are to prevent metastatic spread, preserve kidney function and avoid surgeries

Unmet need /current treatment options

- Repeated surgeries and ablation to kidneys is not an ideal way to manage the condition and need a better alternative
- While death in VHL related to RCC is uncommon due to current treatments, loss of renal function and other VHL-manifestations likely to reduce life expectancy

Quality of life

- Belzutifan targets the key pathway in a precise and effective way and could decrease the burden of kidney surgeries, and reduce damage to other organs (e.g., brain and eye)
- People will benefit from Belzutifan knowing they are having a treatment that is modifying the disease rather than simply removing the tumours

Abbreviations: RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

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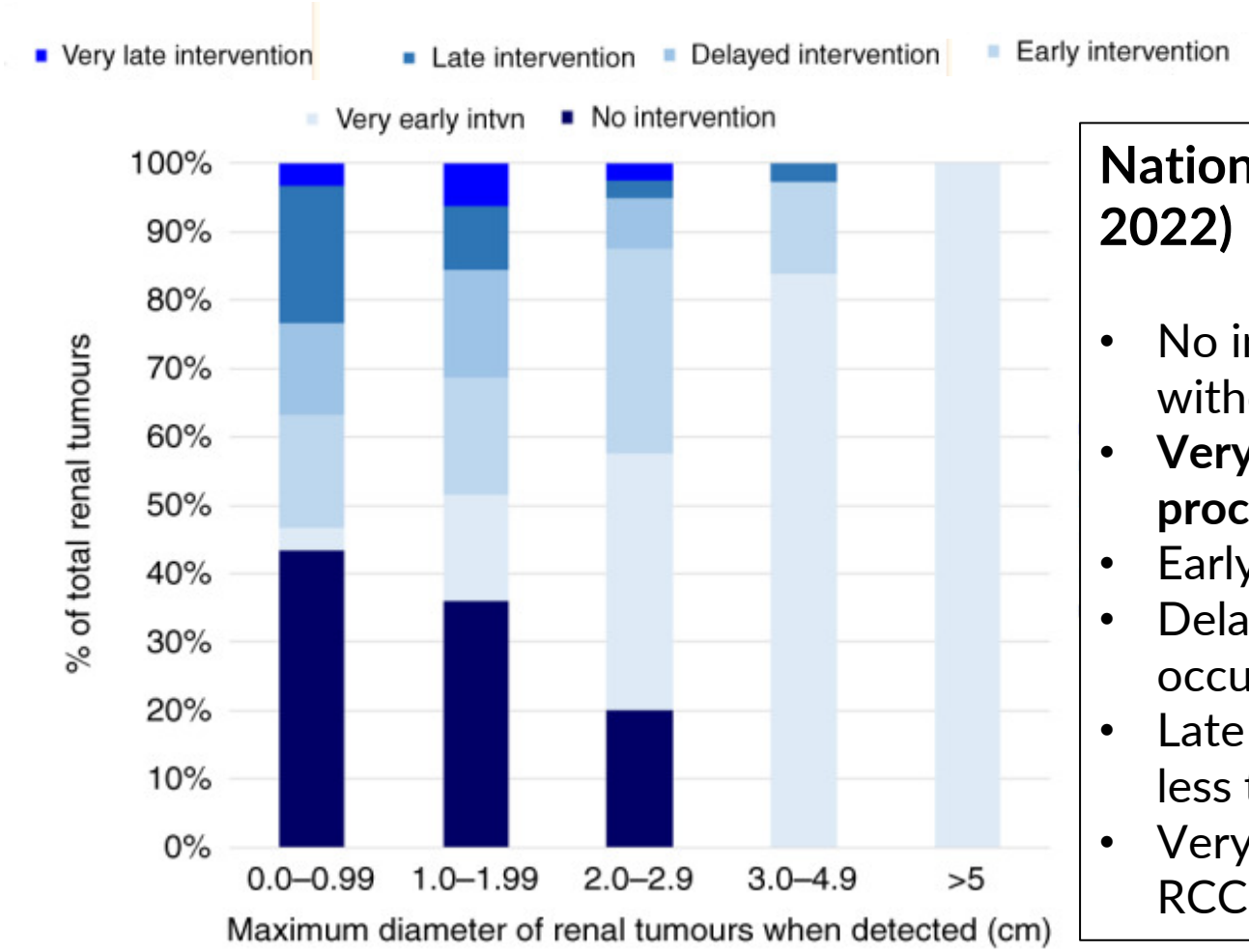
Association between RCC tumour diameter and intervention



National audit of VHL disease in UK (Maher et al 2022)

- No intervention: tumour remained under surveillance without any immediate action
- **Very early intervention: surgical removal or ablative procedure performed within 12 months**
- Early intervention: took place in 12-23 months
- Delayed intervention: refers to when intervention occurred between 3 to less than 5 years
- Late intervention: intervention occurred in between 5 to less than 10 years
- Very late intervention occurred 10 or more years after RCC detection

Please explain the nature of the surgeries in the clinical practice for VHL.
What is the nature of the surgery in terms of life saving and loss of organ function?
Do you consider very early intervention to be the same as immediate surgery?

Abbreviations: RCC, renal cell carcinoma; VHL, Von Hippel Lindau

Number of RCC, CNS Hb and pNET tumours (Maher et al 2022)

842 people diagnosed from 22 UK centres (2012-17)

Tumour type	RCC	CNS Hb	pNET
N= (total 842)	170 (20%)	183 (22%)	36 (4%)
Tumour number	242	217	36
Age (mean, SD/range), years	39.4 (+/- 12.7)	37.04 (9-66)	38.5 (+/- 13.2)
Mean max diameter (cm)	2.16 (SD +/- 1.24)	NA	2.05 (+/- 1.28)
Mean max diameter at 1st scan (cm)	3.07 (+/- 1.28)	NA	2.01 (+/-0.96)
Symptomatic %	NA	38%	NA
Surgery	134 (58%)	NA	15 (41%)*
Ablation/other	44 (19%)	NA	3 (8%)*
Observed	51 (22%)	NA	19 (52%)*
Procedure <12 months	32.3%	NA	NA

*Total > 100% not due to rounding

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Abbreviations: CNS Hb, central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; SD, standard deviation; VHL, Von Hippel-Lindau

VHL treatment timeline for RCC, pNET & CNS Hb

MK-6482-004

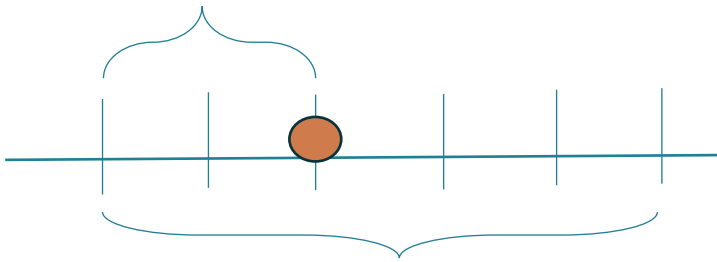
DP population

1. RCC

2. pNET

3. CNS Hb

MRI or ultrasound examinations of the abdomen every 12 months for RCC & pNET



MRI scans of the head for every 12–36 months for CNS HB

1 & 2. Organ-sparing surgery or ablation for RCC & pNET

Belzutifan

1. Based on size of tumour >3cm
2. >2 cm/continued growth
3. Presence of symptoms

Belzutifan

Surgery or radiation (stereotactic radiosurgery)

1. Full bilateral nephrectomy + end stage renal disease
2. Whipple procedure or full pancreatectomy - diabetes
3. Neurological complications (from tumour or surgery)

No surgery + chance of metastasis for RCC & pNET

No chance of metastasis for CNS Hb

MK-6482-004 :no RCC tumour greater than 3.0 cm that requires immediate surgical intervention

DP: tumours which requires therapy reaches 3 cm for RCC and >2-3cm for pNET

What are the criteria for each VHL surgery, and would this be different with Belzutifan?
At what position would treatment with Belzutifan be initiated and how long people would stay on the treatment?

Abbreviations: CNS Hb, central nervous system haemangioblastomas; DP, decision problem; MRI, magnetic resonance imaging; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

Population misalignment

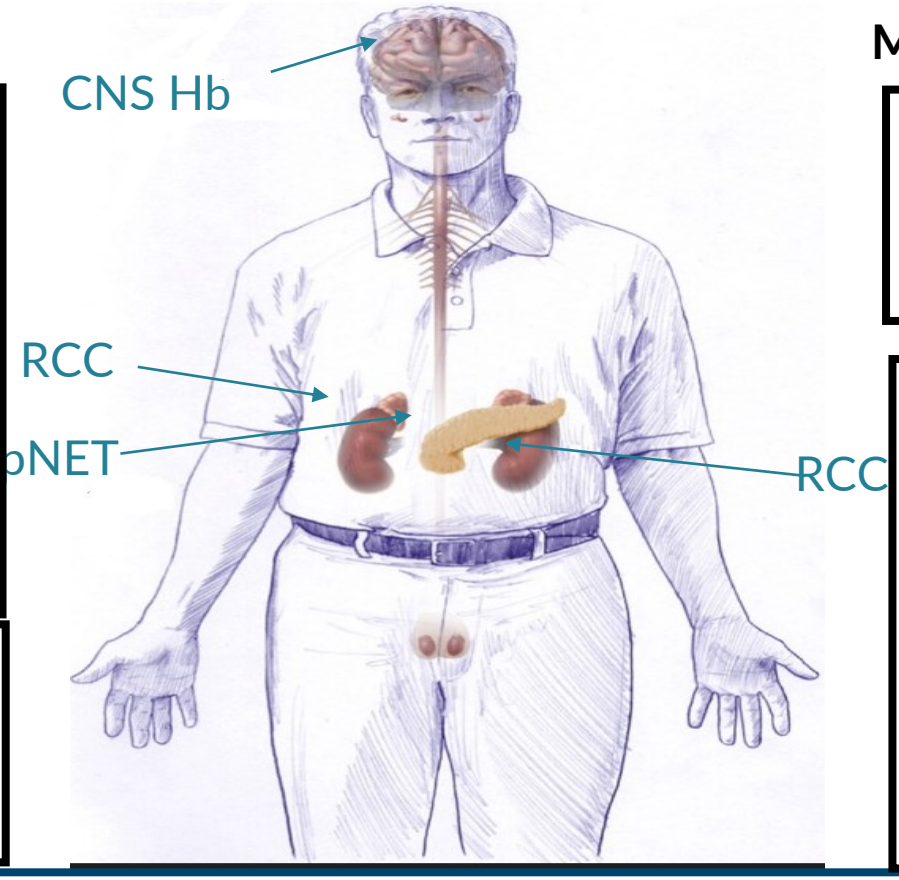
MA: 'Belzutifan is indicated for treatment of adults with VHL disease who require therapy for VHL associated RCC, CNS Hb, or pNET, and for whom localised procedures are unsuitable or undesirable'

DP/MA population

- Adults **≥ 1 VHL related RCC, CNS Hb or pNET**
- Who "require therapy"
  - RCC:> 3cm
  - pNET: 2 cm/continued growth
  - CNS HB: symptoms
- Localised procedures (surgery) "unsuitable/undesirable"

Clinical experts

- Most surgeries in clinical practice are 'urgent' rather than 'immediate'



MK-6482-004

- Adults with **only ≥ 1 measurable only VHL-RCC**
- Not requiring immediate surgery
- No RCC tumour > 3cm

Patient experts

- VHL tumours are slow growing but when begin to cause concern, surveillance should be increased
- 'Immediate' surgery for a VHL patient rarely means 'urgent' or 'emergency

EAG

- Not requiring immediate surgery implies much less severe stage of disease rather than surgery being "unsuitable or undesirable"

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Is the MK-6482-004 trial population reflective of DP population?

Abbreviations: CNS Hb, central nervous system haemangioblastomas ;DP, decision problem; MA, marketing authorisation; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SoC, standard of care

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Clinical trial results: MK-6482-004 (April 2022 data cut-off)

Outcome	Results		
	RCC	CNS Hb	pNET
Primary outcome			
Overall response rate	63.9% (95% CI: 50.6%, 75.8%)	44.0% (95% CI: 30.0%, 58.7%)	90.9% (95% CI: 70.8%, 98.9%)
Secondary outcomes			
Disease control rate (CR + PR + SD)	98.4% (95% CI: 91.2%, 100.0%)	90.0% (95% CI: 78.2%, 96.7%)	100% (95% CI: 84.6%, 100.0%)
Duration of response (median) months	Not reached (range: 5.4 to 35.8)	Not reached (range: 3.7+ to 38.7+)	Not reached (11.0+ to 37.3+)
Time to response (median) months	11.1 (range: 2.7 to 30.5)	[redacted]	[redacted]
Progression-free survival (median)	[redacted]	[redacted]	[redacted]
Time to surgery	Not evaluable	Not evaluable	Not evaluable

NICE What does disease control rate mean in MK-6284-004 vs. DP population?

Abbreviations: CI, confidence intervals; CR: complete response; CNS Hb, central nervous system haemangioblastomas; ORR, over all response rate; pNET, pancreatic neuroendocrine tumour; PR, partial response; RCC, renal cell carcinoma; SD, stable disease

Clinical trial results: PFS & OS for RCC tumours

Median PFS was [redacted]

Company: performing OS analysis based on two deaths out of 61 inappropriate

Figure: Kaplan-Meier plot of PFS for RCC tumours- independent review committee

[redacted]

EAG comments

- Not presenting analysis on OS conflicts b/w study data and outcomes in NICE scope
- Uncertainty remains regarding alignment b/w low number of deaths observed in MK-6482-004 and deaths expected in UK target population

Abbreviations: CI, confidence intervals; OS; overall survival; PFS, progression free survival; RCC, renal cell carcinoma

Establishing relative treatment effect – RCC summary

KM curves fitted for VHL natural history cohort and trial – (naïve comparison)

Adjustment 1

MAIC (reverse)

Fitted curve for SoC is adjusted using an MAIC to match the population in LITESPARK trial – based on variables of age, gender, previous surgeries and tumour size largest solid tumour

Adjustment 2

Standard of care differences

Time to surgery, second surgery and metastasis are adjusted to reflect less active surveillance (than in the trial or VHL natural history study) in the real world – applied to both model arms

Adjustment 3

Apply assumption that 90% of people receive **immediate surgery** (to reflect license wording)

Establishing relative treatment effect – RCC summary

Adjustment 1

- EAG unclear why the population of the VHL cohort was adjusted to match the trial population when both sources of IPD were available
- EAG unclear whether the unanchored MAIC matches on the appropriate confounding variables – does not follow TSD18, unclear of direction or size of bias

What is the value of the MAIC methodology?

Adjustment 2

- Unclear whether standard of care surveillance would result in substantially higher rates of metastasis in the UK

How different is surveillance in the UK compared to specialist USA centres?

Adjustment 3

- EAG considers it implausible that 90% of people would have immediate surgery in the standard of care arm

What is current clinical practice for people that would receive Belzutifan?

Abbreviations: IPD, individual patient data; MAIC; Matching-adjusted indirect comparison; RCC, renal cell carcinoma; TSD, technical support unit document; VHL, Von Hippel Lindau

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Company's model overview

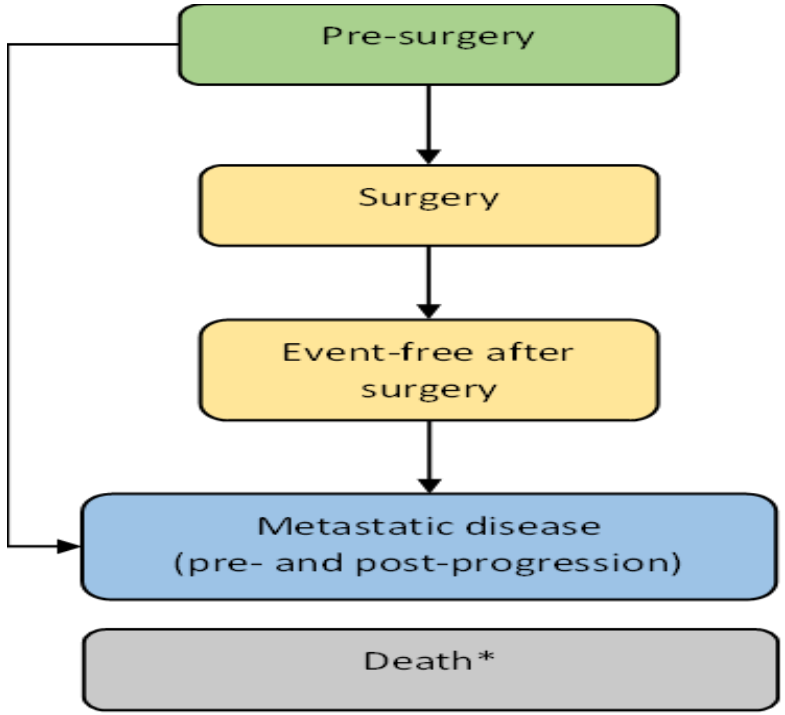


Figure: Model structure

Assumptions with greatest ICER effect:

- Utilities/disutilities in post-surgery health states
- Proportion to receive immediate surgery in SoC arm
- Removal of treatment effect waning
- Distribution chosen to model Belzutifan time on treatment

EAG

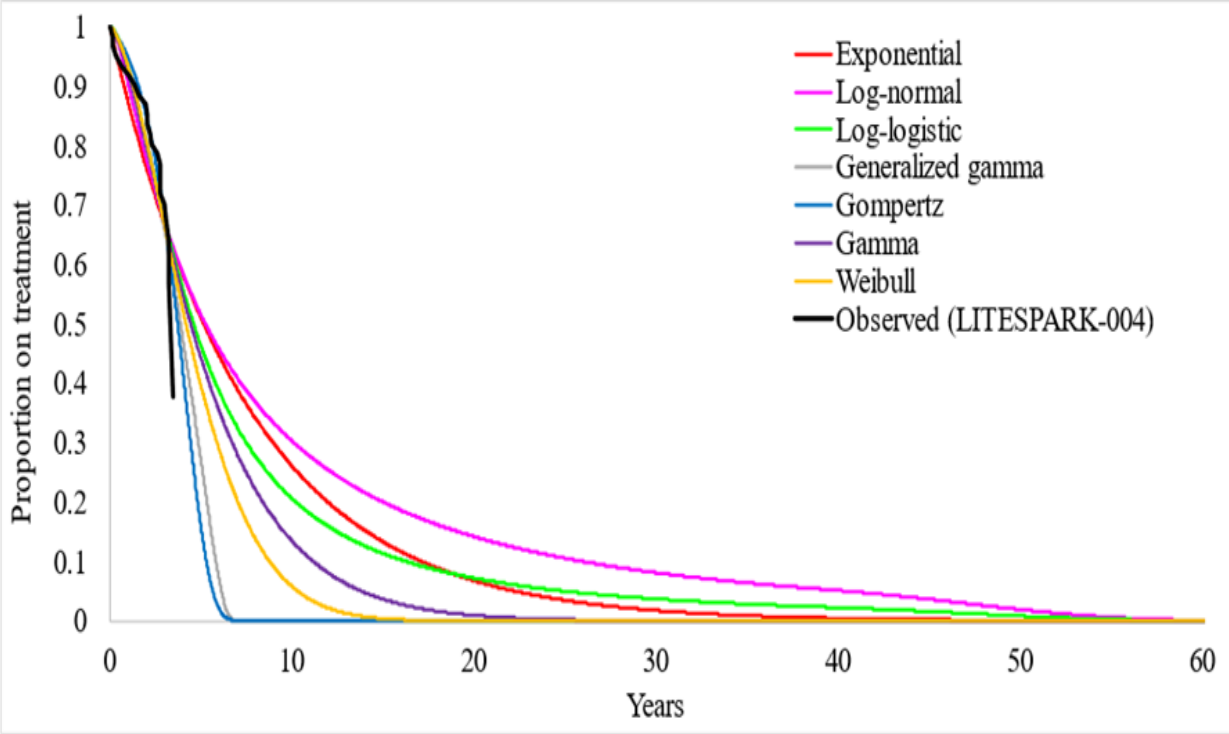
- Company's model appropriate for only VHL RCC and MK-6482-004 populations but **not appropriate** to provide reliable estimates for DP
- Assumptions not validated indicating **large amount of uncertainty**
- Considers **issues relate to data/assumptions** used to inform the model:
  - generalisability to the DP population
  - arbitrary assumptions 90% get immediate surgery for RCC & Pnet
  - doubling perioperative risk to account for 'unsuitable or undesirable'
  - Risk of short and long-term complications adjusted upwards to capture limited organ function following surgery

Technology affects costs by:	Technology affects QALYs by:
Higher unit price compared to standard of care	Decreasing risk of surgery and related complications
Decreasing costs associated to surgery and surgery-related complications	Decreasing risk of metastatic disease
Decreasing costs associated to treating metastatic disease	

Is the company model appropriate for DP population?

Abbreviations: DP, decision problem; ICER, incremental cost-effectiveness ratio; RCC, renal cell carcinoma; VHL, Von Hippel Lindau ; SoC, standard of care

Time on treatment and treatment waning



EAG

- **Parametric fit-** (Gompertz – company base case) to estimate long term ToT for Belzutifan is highly uncertain
- **Treatment effect waning** - Duration of residual benefit after stopping treatment chosen by company as a gradual reduction over 2.71-year period (based on assumptions around a linear growth rate) is also uncertain: could be different for CNS Hb and pNET
- **Data availability** – ToT only used for RCC – hazard ratio approaches used for other transitions in the model

Company TE response

- Agree long term ToT and treatment effect waning uncertain and could be resolved with further readouts from MK-6482-004 if data collected in the CDF

NICE technical team comments

- Unclear if ToT from the trial would reflect clinical practice

When would people stop treatment on Belzutifan? Why did people stop Belzutifan in the trial?

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Abbreviations: CDF, Cancer Drug Fund, CNS Hb, central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; SoC, standard of care; ToT, time on treatment

Derivation and implementation of HRQoL

Health state	Belzutifan	SoC
RCC	0.762	0.728
CNS Hb	0.751	0.695
pNET	0.790	0.728

Table: Response-adjusted overall utility in non-metastatic health states

- Evidence generated from VHL RW QoL disease burden study (all people with VHL, not specific to the decision problem)
- Company considers this represents the best available evidence for people with VHL disease
- Company consider there is an immediate QoL benefit on having Belzutifan in reducing anxiety before a confirmed response
- EAG do not consider this appropriate

Company

- Company also considers additional decrements are appropriate post-surgery: recurring long-term decrements (see table for RCC only), short-term surgical decrements and age-related disutility

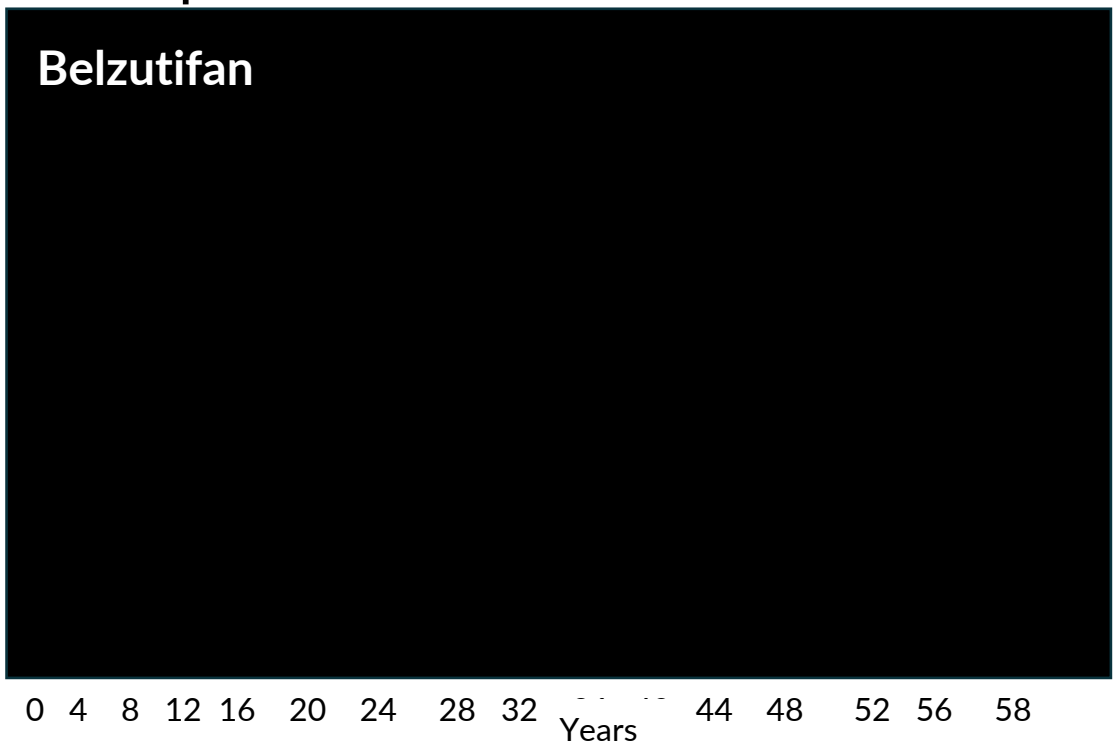
Complication	Risk of surgical complications	Disutility
End stage renal disease and/or dialysis	80.0%	-0.527
Chronic kidney disease	20.0%	-0.136
Hernia	3.2%	-0.200
Chronic pain	17.6%	-0.195
Cerebral vasculature occlusion or stroke	6.4%	-0.370

NICE Is it appropriate to assume immediate benefit for Belzutifan? Are the disutilities appropriate?

Abbreviations: CNS Hb, Central nervous system haemangioblastomas; DP, decision problem; HRQoL, health-related quality of life; pNET, pancreatic neuroendocrine tumour RCC, renal cell carcinoma; RW, real world; SoC, standard of care, TTR, time to response; VHL, Von Hippel Lindau; QoL, quality of life

Modelled output: life-years accrual for Belzutifan vs SoC (RCC)

Time spent in each modelled health state and QALYs generated



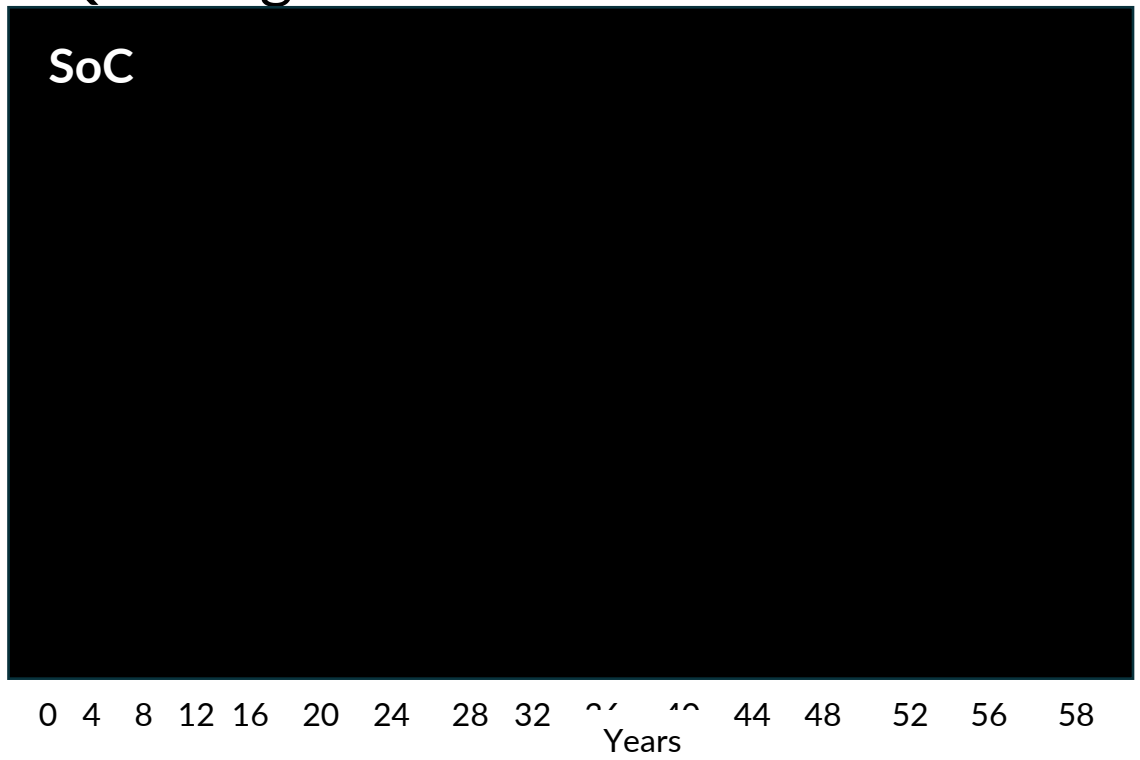


Table: Quality-adjusted life years (QALYs) - undiscounted

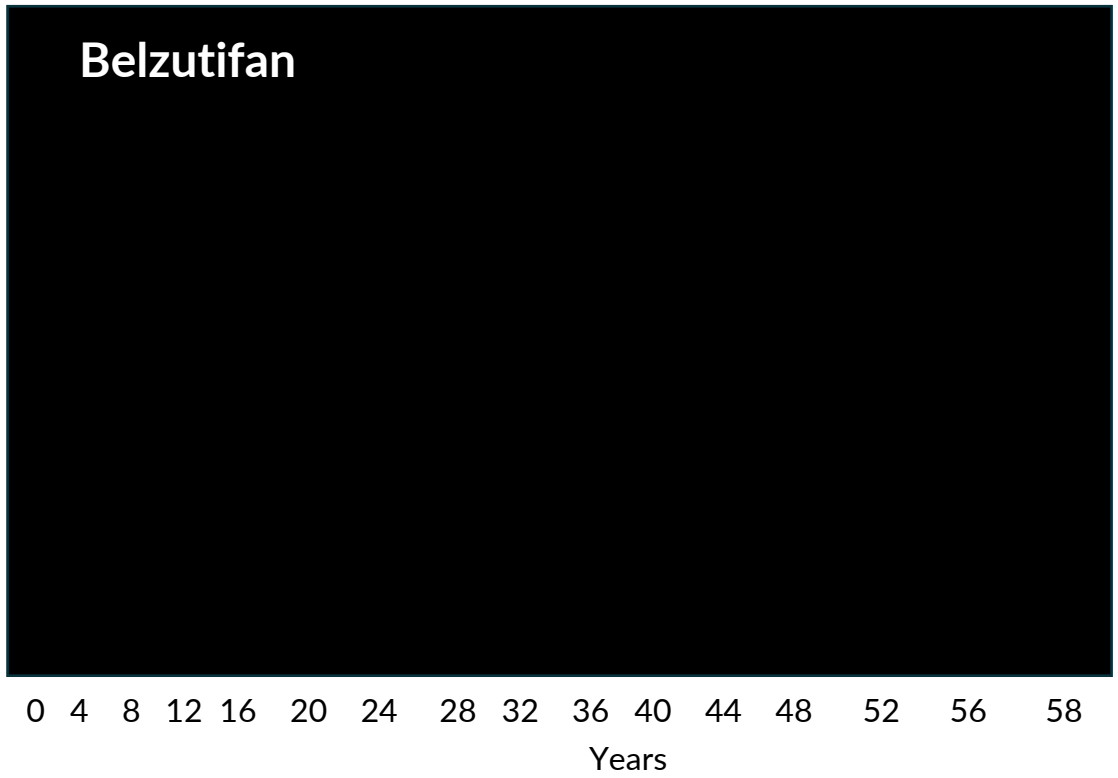
Technology	Pre-surgery	Event-free after surgery	Metastatic disease	Disutility: primary tumour	Disutility: secondary tumours
Belzutifan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

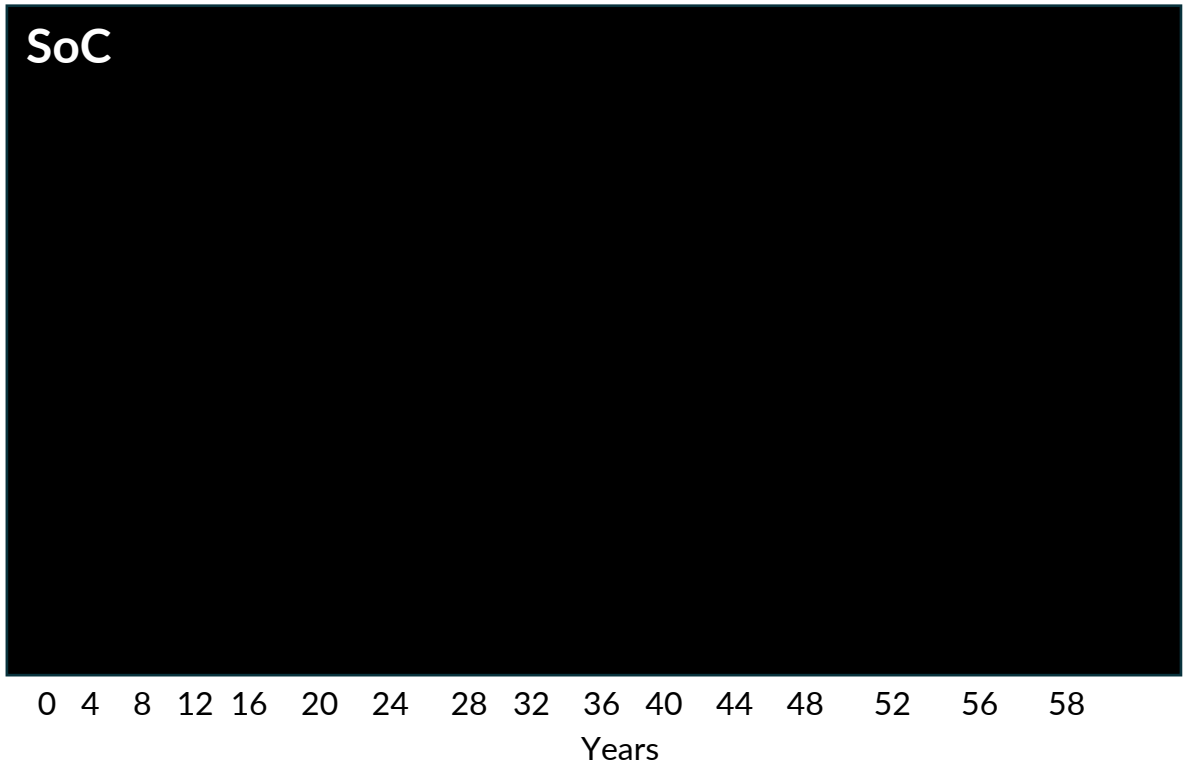
Abbreviation:; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SoC, standard of care

How plausible are the model outputs?
Is it plausible that net benefit of surgery would be indicated by these figures?

Modelled output: life years accrual for Belzutifan vs. SoC (CNS Hb)

Time spent in each modelled health state and QALYs generated





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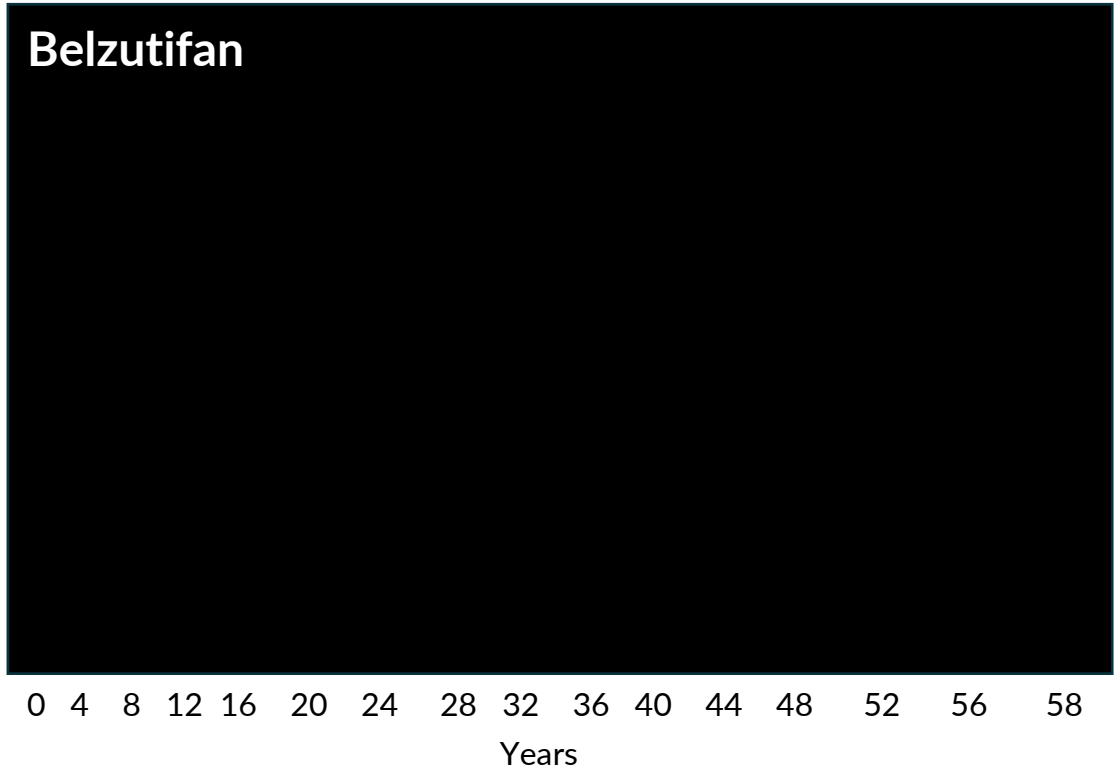
Technology	Pre-surgery	Event-free after surgery	Metastatic disease	Disutility: primary tumour	Disutility: secondary tumours
Belzutifan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: Central nervous system haemangioblastomas; VHL, Von Hippel Lindau; SoC, standard of care

How plausible are the model outputs?
Is it plausible that net benefit of surgery would be indicated by these figures?

Modelled output: life years accrual for Belzutifan vs. SoC (pNET)

Time spent in each modelled health state and QALYs generated



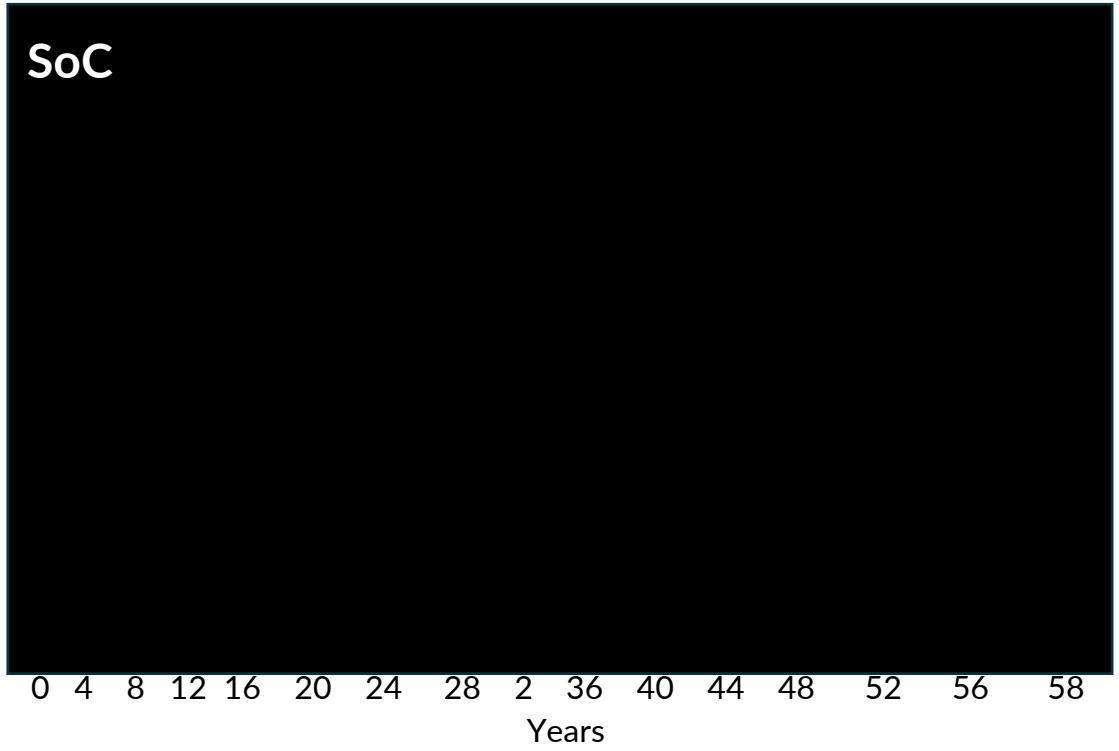


Table: Quality-adjusted life years - undiscounted

Technology	Pre-surgery	Event-free after surgery	Metastatic disease	Disutility: primary tumour	Disutility: secondary tumours
Belzutifan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: pNET, Pancreatic neuroendocrine tumour; VHL, Von Hippel Lindau; SoC, standard of care

How plausible are the model outputs?
Is it plausible that net benefit of surgery would be indicated by these figures?

Severity modifier – calculation and application

Cohort	Total expected QALYs with VHL(SoC)	QALY shortfall		Likelihood QALY Weight (probability weight applicable)
		Absolute	Proportional	
RCC	[redacted]	[redacted]	[redacted]	1.7 (55.9%) ,1.2 (44.1%)
CNS Hb	[redacted]	[redacted]	[redacted]	1.7 (95.4%), 1.2 (4.6%)
pNET	[redacted]	[redacted]	[redacted]	1.7 (1.7%),1.2 (97.5%), 1.0 (0.8%)

- Company considers VHL standard of care has a QALY shortfall that would mean Belzutifan should be considered using the severity modifier
- Each cohort is considered separately in the model, but in the real world would have combined effects so consider a blended QALY shortfall for each cohort
- EAG also provided probabilistic results of applying different QALY weights to demonstrate that application may be different for different cohorts – and focus should be on the population in the license

NICE technical team comments

- Consider severity with caution because of high level of uncertainty in SoC

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What is the appropriate severity modifier for Belzutifan? How should shortfall be calculated for 3 separate cohorts or combined?

Abbreviations CNS Hb, Central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; QALY, quality adjusted life years; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SoC, standard of care

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Other considerations

Equality considerations

- No equality issues were raised by the company but highlighted some families are disproportionately affected and can affect people when they are very young
- Stakeholders identified people from deprived areas, with language, learning or cultural barriers, or those with disabilities may be at a disadvantage

Innovation

- Belzutifan has obtained regulatory approval via the MHRA ILAP pathway (reserved for innovative medicine which are aimed to address very high unmet need)
- Company consider some additional benefits not fully captured in the model

Potential for managed access

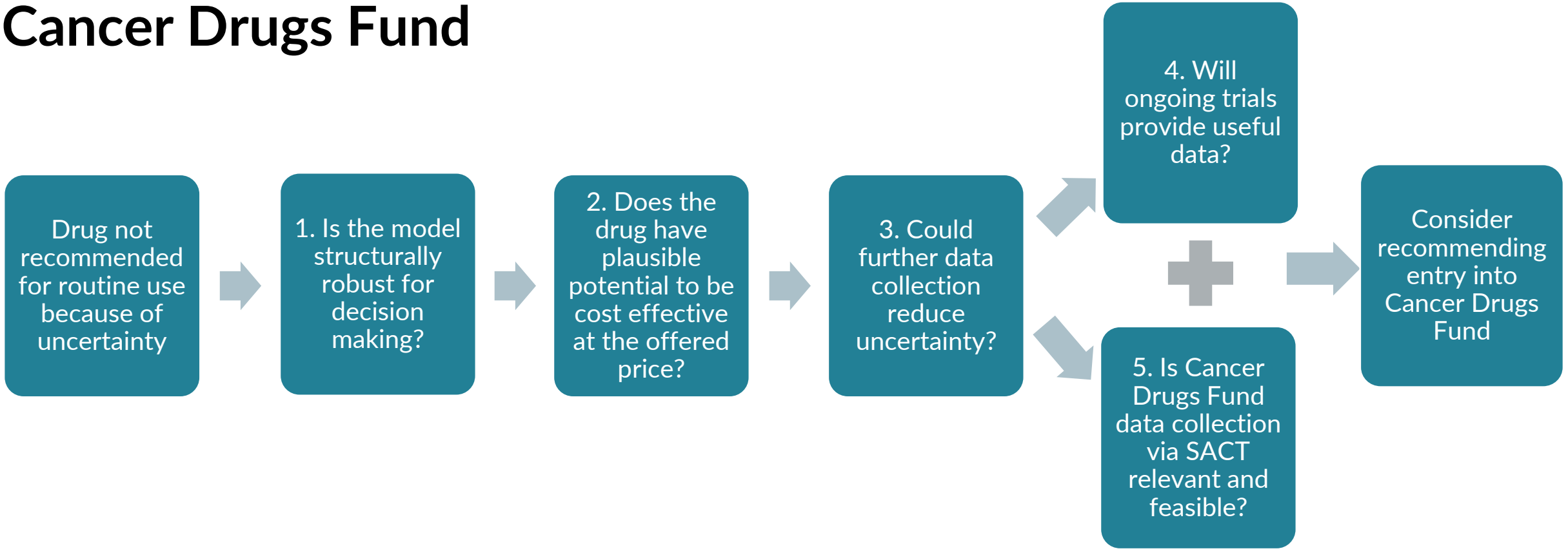
- Managed access proposed by the company: risk to NHS and patients can be mitigated by a rapid Cancer Drugs Fund (CDF) recommendation
- Company consider additional uncertainties will best be resolved through data collection via the CDF

Rarity

- Committee should be mindful that for rare disease, evidence generation may be particularly difficult - In these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty. The committee will consider how the nature of the condition affects the ability to generate high-quality evidence before applying greater flexibility

Abbreviations: ACM, appraisal committee meeting; CDF: Cancer Drugs Fund; MHRA, Medicines and Healthcare products Regulatory Agency; ILAP, Innovative Licensing and Access Pathway

Cancer Drugs Fund



- Company: Belzutifan is a suitable candidate for the CDF: No additional data will be available b/w ACM1 and ACM2
- Would the issues discussed be resolved through further data collection for e.g. uncertainty around effectiveness, treatment duration treatment effect waning in MA population

Is Belzutifan a candidate for CDF?

Abbreviations: ACM, Appraisal committee meeting; CDF, Cancer Drugs Fund; MA, Marketing Authorisation; SACT, Systemic Anti-Cancer Therapy

Questions for clinical experts

- Please explain the nature of the surgeries in the clinical practice for VHL? – See slide
- Do you consider very early intervention to be the same as an immediate surgery? – See slide
- What are the criteria for each VHL surgery, and would these apply to Belzutifan given it reduces risks of surgery? See slide
- At what position would treatment with Belzutifan be initiated? See slide
- How long people stay on the treatment with Belzutifan? See slide
- What is current clinical practice for people that would receive Belzutifan? See slide
- How different is surveillance in the UK compared to specialist USA centres? See slide
- Is the MK-6482-004 trial population reflective of DP population? See slide
- What does disease control rate mean in MK-6284-004 vs. DP population? See slide

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Abbreviations: DP, decision problem; VHL, Von Hippel Lindau

Committee decision making slide

Assumption	Question for committee
Population misalignment	Is the company's population relevant to the DP/MA population?
Company's ITC	Is the company's approach to ITC appropriate?
Health related quality of life	Is it appropriate to assume immediate benefit for Belzutifan? Are the disutilities appropriate?
Time on treatment and treatment effect wanning	Is the company's approach to implement ToT and treatment effect wanning appropriate
Severity modifier	What is the appropriate severity modifier for Belzutifan? How should shortfall be calculated for 3 separate cohorts or combined?

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Abbreviations: DP, decision problem; ITC, indirect treatment comparison; MA, marketing authorisation; SoC, standard of care; VHL, Von Hippel Lindau

Cost-effectiveness results

All ICERs are reported in PART 2 slides

- Company base case and scenarios
- EAG unable to define base case due to uncertainties in the evidence

Belzutifan for treating tumours associated with Von Hippel-Lindau disease

Supplementary appendix

NICE National Institute for Health and Care Excellence

Belzutifan (Welireg, MSD)

Table: Technology details

Marketing authorisation	'Belzutifan is indicated for treatment of adults with von Hippel-Lindau (VHL) disease who require therapy for VHL associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable'
Mechanism of action	• Belzutifan targets hypoxia inducible factor (HIF) - 2α • By blocking the activity of HIF-2α, Belzutifan slows down worsening of VHL and improves symptoms
Administration	• Oral: 120 mg (3X 40mg tablets once daily with or without food) • Treatment should continue until disease progression or unacceptable toxicity occurs
Price	• List price, £11,936.70 for 90 tablets (40 mg) • Average cost of treatment : [redacted] • There is a proposed simple patient access scheme (PAS) discount for Belzutifan

Abbreviations: VHL, Von Hippel-Lindau

Decision problem (1/2)

	Final scope	Company decision problem/EAG comments
Population	Adults who require therapy for RCC, CNS Hb, or pNET tumours caused by VHL, for whom localised procedures are unsuitable/ undesirable	Adult patients with VHL disease who require therapy for VHL associated RCC, CNS hemangioblastomas, or pNET, and for whom localised procedures are unsuitable or undesirable **Company and EAG** agreed misalignment between the DP/MA and MK-6482-004 study populations
Intervention	Belzutifan	Belzutifan **In line with the NICE scope**
Comparators	**RCC, CNS Hb & pNET:** • SoC without Belzutifan **RCC:** • For advanced or metastatic disease, monotherapy or combination therapy with immunotherapies or kinase inhibitors **pNETs** • For unresectable/metastatic disease, monotherapy with lutetium oxodotreotide or combination with everolimus and sunitinib	For VHL associated RCC, pNET, and CNS hemangioblastomas: • Current SoC without Belzutifan **Company** considered no treatments for advanced or metastatic disease are relevant as comparators because these would be used after treatment with Belzutifan

Abbreviations: CNS Hb, Central nervous system haemangioblastomas; DP, decision problem; MA, marketing authorisation; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; SoC, standard of care

Decision problem (2/2)

	Final scope	Company decision problem/EAG comments
Outcomes	• Overall survival • Progression-free survival • Response rates • Tumour size reduction • Reduction in number of surgical interventions • Adverse effects of treatment • HRQoL	• Response rates • Reduction in number of surgical interventions • Adverse effects • Progression-free survival • Tumour size reduction **Company** • Overall survival was not a designated predefined outcome in the MK-6482-004 • HRQoL not collected in MK-6482-004 • OS and HRQoL derived from other sources **EAG** • Outcomes driven based MK-6482-004 data: **Not in line with NICE scope**

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Abbreviations: HRQoL, health-related quality of life

Issue 1: Difference between intervention & comparator populations 1/2

Background

- Contradiction between intervention and comparator populations description specifically:
  - Localised procedures (surgery) are considered unsuitable or undesirable for DP/MA population while for comparator (SoC) population the surgery must be delivered immediately
  - If Belzutifan administered there is no immediate surgery even it is needed: contradicts clinical practice
- EAG consider intervention and comparator should be identical: %age of people having immediate surgery should be same for both arms i.e., if no Belzutifan eligible people are receiving surgery then no such surgery should be given for SoC

Company

- Clarified Belzutifan was granted MA in UK via Orbis route, i.e., a regulatory application linking the MHRA process with FDA regulatory process and how MHRA restricted population for whom localized procedures are unsuitable or undesirable
- Clinical opinion to company: people who require therapy are not suitable for active surveillance and require an intervention which is surgery in UK in absence of Belzutifan
- Technically appropriate for all people in SoC to have surgery and clinical experts disagreed about EAG's concern about delaying surgery in model

Abbreviations: DP, decision problem; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; SoC, standard of care

Issue 1: Difference between intervention and comparator populations 2/2

Company

- People with VHL unlikely to undergo surgery, any delay in treatment decision and actual treatment is due to practical and NHS scheduling issue which are hard to model
- Disagree Belzutifan-treated people should also receive immediate surgery to reduce any immediate harm as people have the option an effective therapy which as would render Belzutifan an adjuvant therapy not in line with MA
- Consider majority of RCC tumours reduced soon after initiation of treatment with Belzutifan (12 weeks)*

Clinical experts

- "Most surgeries in clinical practice are urgent rather than 'immediate' which needs carefully planning within a weeks"

Patient experts

- VHL tumours are slow growing but when begin to cause concern, surveillance should be increased
- 'Immediate' surgery for a VHL patient rarely means 'urgent' or 'emergency'

Is it appropriate to assume immediate surgery in SoC and not for Belzutifan

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Abbreviations: MA, marketing authorisation; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau ; SoC, standard of care

*See appendix – slide 48

Issue 2 : Population misalignment b/w DP & MK-6482-004

EAG: MK-6482-004 not generalisable to UK target population

Background

- MK-6482-004 population was narrower than DP population (≥1 RCC, in contrast to ≥ 1 RCC, CNS Hb or pNET)
- MK-6482-004 also had less severe disease than DP; not generalisable to UK population

Company

- Acknowledged DP/MA population differed from MK-6482-004 study
- VHL is heterogenous disease, people with VHL associated CNS Hb or pNET are likely to have RCC tumours so considers MK-6482-004 results representative of UK practice
- Also clinical experts confirmed MK-6482-004 representative of VHL disease in UK and they can clearly identify Belzutifan-eligible population as per indication
- Agreed some people in MK-6482-004 have less severe disease but this is common; unethical to deny surgery to people with immediate need for surgery
- Clinical experts believe Belzutifan-eligible people in DP are at an advanced stage and would experience organ function loss or impairment despite the need for surgery

EAG TE response

- Concerned that Belzutifan eligible also require surgery but they must wait until disease response, which challenges company's claim that people can wait for Belzutifan's outcome before having surgery

Is the company's population generalisable to DP population?

Abbreviations: CNS Hb, central nervous system haemangioblastomas; DP, decision problem; MA, marketing authorisation; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

Issue 3: potential risk of study selection bias resulting in possible omission of relevant comparator studies

Background

- Company's SLR identified 26 studies but only one (MK-6482-004) was used. EAG considers remaining 25 studies could have provided relevant comparator
- EAG concerned about discrepancies regarding interventions, comparators and outcomes: specifically, surgery categorised differently creating uncertainty
- SLR excluded case series & limited inclusion to English language adding uncertainty and bias

Company

- No additional clinical effectiveness data available for Belzutifan in this indication beyond MK-6482-004, so no trial-based indirect treatment comparison Belzutifan with other regimens is possible
- No other studies examining any other treatment provide data representative of UK SoC for this indication, so VHL study was commissioned to provide information for comparator arm prior to MA
- Explained 2 non-English publications does not provide data on Belzutifan and SoC for UK and search strategy were designed to identify all relevant interventional, non-interventional and natural history studies

EAG TE response

- Concerned about lack of clarity why a treatment that does not represent UK practice is deemed uninformative given there is no evidence of effectiveness of what company standard practice (immediate surgery)

Abbreviations: MA, marketing authorisation; SLR; systematic literature review; SoC, standard of care; VHL, Von Hippel Lindau

Key clinical trial: MK-6482-004

EAG: MK-6284-004 population not representative of DP population

	MK-6482-004	
Design	Phase II, open label, single-arm	
Population	People with VHL disease who have at least one measurable RCC tumour	
Intervention	Belzutifan	
Duration	Until unacceptable treatment-related toxicity or unequivocal disease progression	
Primary outcomes	Overall response rate (complete or partial defined RECIST 1.1)	
Secondary outcomes (used in model)	• Duration of response, time to response, progression-free survival, time to surgery, adverse events	
Key Inclusion exclusion criteria	Inclusion • Diagnosis of VHL disease • At least 1 measurable solid RCC tumour and no RCC tumour greater than 3.0 cm that requires immediate surgical intervention	Exclusion • Had a surgical procedure for VHL disease or any major surgical procedure completed within 4 weeks prior to study enrolment • **Had an immediate need for surgical intervention for tumour treatment**
Locations	Multicentre, 11 sites in Denmark, France, UK and US	

Abbreviations: DP, decision problem; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours VHL, Von Hippel Lindau; VEGF (vascular endothelial growth factor

Baseline characteristics: MK-6284-004

EAG: MK-6284-004 population not representative of UK target population

Table: MK-6284-004 baseline characteristics

Baseline characteristics		Belzutifan (n=60)
Age (mean), years		31.3 (14.29)
VHL subtype, n (%)	Type 1	51 (83.6)
	Others (Type 2A,2B & missing)	10 (16.4)
VHL-associated Non-RCC tumours, n (%)	Pancreatic lesions	32 (52.5)
	Pancreatic lesions; pNETs	22 (36.1)
	Adrenal lesions (pheochromocytomas)	3 (4.9)
	CNS Hb	51 (83.6)
	Endolymphatic sac tumours	1 (1.6)
	Epididymal cystadenomas	10 (16.4)
	Retinal lesions	17 (27.9)
	Other	2 (3.3)
Number of prior Surgeries	n	59
	Mean (SD)	5.5 (3.34)

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Are these baseline characteristics generalisable to NHS clinical practice?

Abbreviations: CNS Hb, central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SD, standard deviation

How company incorporated evidence into model

	Assumptions and evidence source
Time horizon	• Lifetime (59 years)
Intervention efficacy	• Health state TPs and surgery incidence from the MK-6482-004 trial
Comparator efficacy	• Initial risk of surgery based on definition of target population and reflects treatment decision point at which Belzutifan becomes a treatment option • Remaining transition probabilities are sourced from VHL Natural History Study (adjusted using Optum study) and analysis of pre-treatment phase MK-6482-004
Utilities	• Health state utilities in pre-surgery, surgery and event-free after surgery were calculated as a weighted average of EQ-5D utility values for CR (KEYNOTE-564 trial), PR/SD (sourced from VHL RW QoL Study) • PR and SD assumed to be equal, and PD (sourced from the VHL RW QoL study • Disutilities relating to short-term and long-term consequences of surgery were applied to event-free-after surgery state
Costs	• Belzutifan: drug acquisition and administration costs • Metastatic disease therapies, health states, costs associated to surgery and its complications, AEs, and other costs
Resource use	NHS Reference Costs, PSSRU, BNF and Monthly Index of Medical Specialties (2020/2021)

Abbreviations: BNF: British National Formulary; CR, complete response; HRQoL, health related quality of life; PR, partial response; PSSRU: Personal Social Services Research Unit ; VHL, Von Hippel Lindau; SoC, Standard of Care; SD, stable disease; TP, transition probabilities

Issue 4: Lack of link b/w clinical and cost-effectiveness sections

Background

- VHL study was used for clinical effectiveness for SoC while data from pre-treatment phase of MK-6482-004 and Optum study was for used cost-effectiveness section
- Comparison of three should have been presented to allow assessment for an ITC for time to event outcomes

Company

- Pre-treatment phase of MK-6482-004 was used calculate transitions in model for pre-surgery to first surgery/metastasis/death and no ITC/MAIC was required
- VHL study could not identify people with RCC and pNET or with CNS-Hb at index date, so data from pre-treatment phase of MK-6482-004 was used for pre-surgery to first surgery rates
- Optum Clinformatics study was designed to derive inputs for economic model but not for direct comparison with MK-6482-004 as the outcomes from Optum were not same as MK-6482-004; making it inappropriate to compare/combine data from these two studies in ITC/MAIC
- Highlighted limitations of using Optum data for constructing external arm including :
  - Limited availability of matching variables and ability to measure number of prior surgeries
  - Identifying people with VHL disease (VHL ICD code was introduced recently)
- Consider adjusted/reweighted results from VHL study provide well matched model parameters

EAG TE response

- Company misunderstood purpose of the clinical effectiveness evidence and any ITC for to used and considers it a key issue as the company have not any further explanation

Abbreviations: CNS Hb, Central nervous system haemangioblastomas; ICD; International Classification of Diseases; ITC, indirect treatment comparison; MAIC, Matching-Adjusted Indirect Comparison pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; SoC, standard of care

Issue 6: Population misalignment b/w economic analyses and source of evidence

Background

- EAG consider mismatch b/w population in economic analyses and sources of evidence specifically:
  - Type of tumour: model distinguishes cohorts by tumour type which is not possible based on MK-6482-004 as it does not distinguish if tumour is primary or not
  - Severity: no evidence in people for whom surgery is "unsuitable or undesirable" (DP population); and surgery rates in MK-6482-004 trial may be underestimated compared with DP population
  - Arbitrary assumptions: 90% of people having immediate surgery in SoC; perioperative mortality risk; short- and long-term complications following surgery
  - Harm and benefits for having or not having immediate surgery not captured in model

Company TE response

- Issue only relevant if objective response rate of MK-6482-004 differ from DP population
- Acknowledged challenges and limitations in modelling due to lack of data and VHL heterogeneity
- Some aspects of patient experience in VHL not captured; thus underestimating the true cost-effectiveness of Belzutifan as model also does not account for multi-system tumours
- Model also did not capture impact of the disease on families where multiple members are affected with varying presentations and have limited treatment options
- Reiterated positive CDF will help to address uncertainties in modelling the decision problem population

Would further data collection resolve the uncertainties in relation to populations?

Abbreviations: CDF, Cancer Drug Fund; DP, decision problem; VHL, Von Hippel Lindau; SoC, Standard of Care

Issue 7 : Comparator data not representative for UK

EAG

- Company adjusted transition probabilities in model include pre-surgery to surgery, pre-surgery to metastases and event-free after surgery to metastases in both arms as considered people in US-based VHL study and MK-6482-004 received higher quality SoC compared with UK clinical practice
- Optum study data (US based) were used for these adjustments, specifically for surgery and metastases rates in RCC cohort while adjustments to metastases rated only for CNS Hb and VHL pNET cohorts; Company further lowered the surgery rates to those observed in MK-6482-004 study
- But people with more severe disease may face greater risk of surgery and metastasis, and efficacy of Belzutifan in more severe population unclear
- Considerable uncertainty in the treatment effect as modelled by the company

Company TE response

- Acknowledged MK-6482-004 and VHL natural history study received elevated care compared to UK, but this was addressed using Optum study which analysed treatment pattern and resource use for VHL claims data
- Experts validated this data to adjust surgery & metastases rates in model which were made to both arms
- Consider removing Optum study adjustment does not have impact on decision making
- Acknowledged uncertainties using US data and highlighted use of international data is common in technology evaluations which should not stop NICE in making access decisions
- CDF recommendation would allow data collection to begin to address these concerns

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Does MK-6482-004 reflect UK practice or should an adjustment be made?

Abbreviations: DP, decision problem; MA, marketing authorisation; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma

Issue 9: Uncertainty in derivation of transition probabilities in SoC

Background

- Pre-treatment data from MK-6482-004 were used to inform transitions from pre-surgery to surgery in CNS Hb and pNET cohorts in SoC arm
- EAG considers approach potentially biased as different sources used to define transitions within same cohort
- EAG: due to differences in incidence rate for VHL RCC cohort between VHL history study and pre-treatment of MK-6482-004; pre-surgery to surgery rates for CNS Hb and pNET in SoC could be underestimated

Company

- Pre-treatment phase of MK-6482-004 could not be used to estimate transitions for metastases and death; people had to be alive and metastases-free to be eligible to participate in trial, so VHL history study was used
- Consider VHL history study most appropriate source for RCC cohort; provides consistency through out
- EAG's scenario of doubling risks from pre-surgery to surgery in SoC for CNS Hb & pNET does not account for fact people can have multiple tumours across two kidneys; different from pancreatic and CNS surgeries

Table: Parameter values for SoC in RCC subgroup using the MK-6482-004 pre-treatment data

Parameter		VHL study	MK-6482-004 pre-treatment
Weekly rate of pre-surgery to RCC surgery		0.00487	0.00207
Weekly rate of non-RCC tumour surgeries		0.00344	0.00438
Surgeries for non-RCC tumours	**CNS Hb**	52.4%	67.4%
	pNET	3.4%	7.0%

Abbreviations: CNS Hb, central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; SoC, standard of care; VHL, Von Hippel Lindau

Issue 8 : Data to inform effectiveness in the Belzutifan arm (MK-6482-004 trial) are either immature or unavailable

Background

- Data from MK-6482-004 immature for three VHL cohorts especially for pNET and CNS Hb cohort:
  - Transition probabilities from pre-surgery health state in Belzutifan estimated from MK-6482-004 data but trial population does not match DP population
  - Also were based small number of observed surgery and metastatic events or derived from other assumptions: indicating high uncertainty in MK-6482-004 and company's survival analyses

Company

- Median follow-up of 37.7 months from 61 people (April 2022-datacut) should not be considered immature
- VHL not a typical cancer so focus should be on number of surgeries rather than data immaturity
- Long-term effectiveness for Belzutifan can be resolved by further data collection through CDF and MK-6482-004 will provide safety and efficacy data until 2026
- Consider EAG scenario using Gompertz to extrapolate Belzutifan arm is implausible (curves cross)
- In absence of an EAG-preferred parametric function company base-case (exponential) should be accepted

EAG TE response

- Reiterate uncertainty in long-term extrapolations of treatment effectiveness: more UK practice data needed
- Alternatives parametric distributions explored by EAG shows Belzutifan cost-effective but results should be considered with extreme caution as none of distribution are reliable

Abbreviations :CDF, Cancer Drug Fund; DP, decision problem; VHL, Von Hippel Lindau; SoC, Standard of Care

Indirect treatment comparison (ITC) methodology and results

- Company MAIC using MK-6482-004 & VHL study to compare Belzutifan with SoC to inform CEA
- RCC indication VHL Natural History Study data closely matched the MK-6482-004
- CNS Hb & pNET indications, people who met inclusion/exclusion criteria were further restricted to those with a recorded history of CNS Hb and pNET: but faced challenges in identifying people at patient level index
- For people not receiving immediate surgery, TTS estimated from pre-treatment phase of MK-6482-004 for SoC
- Clinical effectiveness of VHL study only reported outcomes for RCC cohort (TTS & non-RCC VHL-related surgeries with therapeutic intent). Despite, this company made adjustment to all three cohorts not just RCC

Table: Reweighted VHL Natural History Study RCC cohort and the MK-6482-004 trial population outcomes

Outcomes	VHL Natural History study (N=92.2*)	MK-6482-004 (n=61)
Exponential rate parameter for cause-specific hazards of pre-surgery → 1st surgery		
Rate (events/person-year)	0.25324	0.03692
Standard error	(0.01768)	(0.0156)
Incidence of non-RCC VHL-related surgeries with therapeutic intent (events/person-year)		
Number of VHL-related surgeries	2116.4	208
Total person-years at risk	227.35	194.41
Incidence rate (events/person-week)**	0.178984	0.02119

Abbreviations: ITC, indirect treatment comparison; MAIC, Matching-Adjusted Indirect Comparison; RCC, renal cell carcinoma; SoC, standard of care, TTS, time to surgery, VHL, Von Hippel Lindau;

*After matching
** EAG corrected person-week

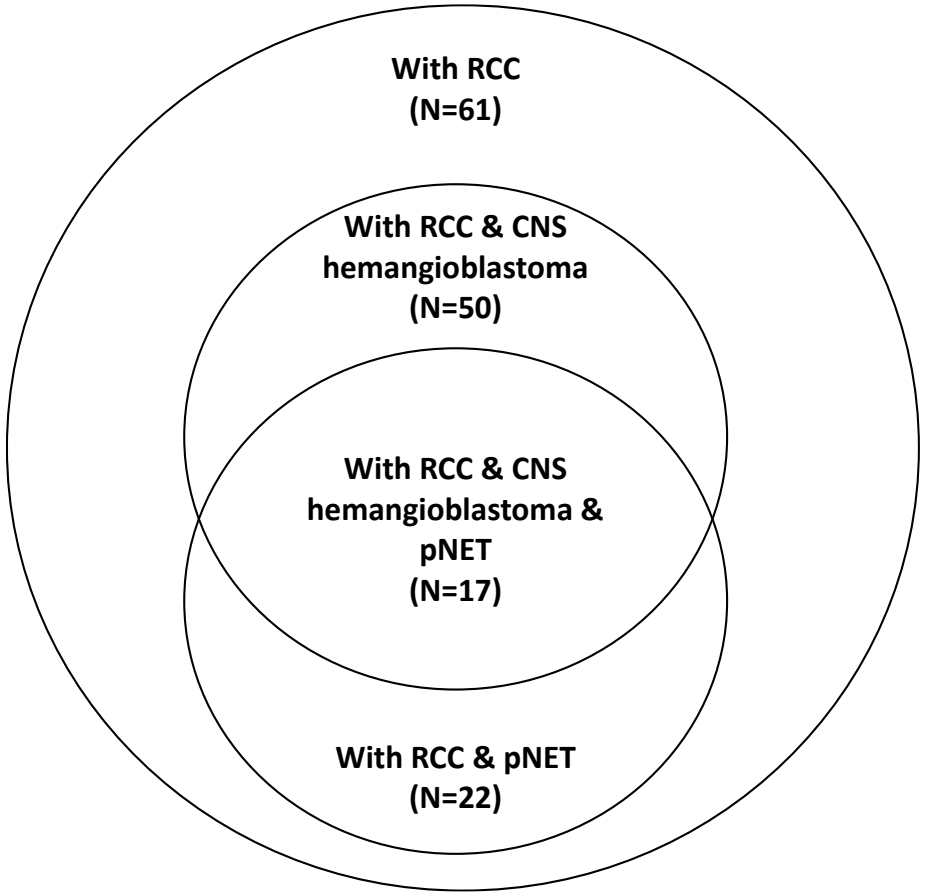
Difference between intervention and comparator populations

Company: MK-6284-004 indicate that Belzutifan's onset of efficacy is rapid detectable at 12 weeks; [redacted] people had a reduction in total sum of RCC target lesions trial diameters

Figure: Spider plot – Percentage change in total sum of RCC target lesion diameters from baseline in scan before and after treatment – investigator assessment

Abbreviations: RCC, renal cell carcinoma; SoC, standard of care; VHL, Von Hippel Lindau

Summary of subgroups : MK-6482-004 study



MK-6482-004 include 61 people with RCC out of which:

- 50 of 61 people with RCC had CNS hemangioblastomas
- 17 of the 50 patients with RCC and CNS hemangioblastomas also had pNETs
- 22 of the 61 patients with RCC also had pNETs

Abbreviations: CNS Hb, central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; SoC, standard of care; VHL, Von Hippel Lindau

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Back up