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# HEALTH TECHNOLOGY BRIEFING JANUARY 2021

# Belzutifan for von Hippel-Lindau disease-associated clear cell renal cell carcinoma – first line

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| **NIHRIO ID** | 30386 | **NICE ID** | 10540 |
| **Developer/Company** | Merck Sharp & Dohme | **UKPS ID** | 657441 |

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| **Licensing and market availability plans** | Currently in phase II clinical trials. |

## SUMMARY


Belzutifan is in clinical development for the treatment of von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC). VHL is a hereditary disease that results in the body producing an increased amount of the protein hypoxia inducible factor (HIF) - 2α. This leads to an increased risk of tumours developing in various parts of the body including the kidney. Renal cell carcinoma (RCC) is the most common type of kidney cancer. ccRCC is named as such because when this type of tumour is viewed under a microscope the cells appear clear. Currently patients with VHL disease have limited treatment options which focus on surgically removing tumours once they have developed.

Belzutifan is a first-in-class drug that is taken orally and works by selectively blocking the activity of the HIF-2α protein. HIF-2α plays a role in cancer cell survival, cell growth and blood vessel formation so by blocking this protein belzutifan is thought to slow down the worsening of the disease and improve symptoms. If licensed, belzutifan may offer an additional treatment option for patients with VHL disease-associated ccRCC.

# PROPOSED INDICATION

First line treatment of von Hippel-Lindau (VHL) disease-associated clear cell renal carcinoma (ccRCC).[1]

# TECHNOLOGY

## DESCRIPTION

Belzutifan (MK-6482, PT2977) is a first-in-class oral drug that works by selectively blocking the activity of a protein called hypoxia inducible factor (HIF) - 2α which accumulates when the oxygen levels in cells are low.[2,3] HIF-2α promotes cell survival, cell growth and formation of new blood vessels. HIF-2α levels are raised in patients with VHL disease even when oxygen levels are normal. Therefore, by blocking the activity of HIF-2α, it is expected that belzutifan will slow down worsening of the disease and improve symptoms.[3]

Belzutifan is currently in clinical development for the treatment of VHL disease associated ccRCC. In the phase II clinical trial (NCT03401788) participants are given 120mg belzutimab once daily in the form of three oral 40mg tablets.[1]

## INNOVATION AND/OR ADVANTAGES

Currently there are no satisfactory methods authorised for treating VHL disease. Belzutifan would be the first therapy approved for the treatment of VHL as opposed to surgery to remove tumours associated with VHL.[3] There is a need to develop additional treatment options for patients with VHL disease-associated ccRCC.

Belzutifan is a novel drug that has shown promising efficacy and tolerability in participants with VHL-associated ccRCC.[4]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Belzutifan does not currently have Marketing Authorisation in the EU/UK for any indication.

Belzutifan was granted orphan drug designation by the EMA in August 2020 for the treatment of VHL disease.[3]

Belzutifan is also in phase II and III clinical development for the treatment of renal cell carcinoma (RCC) that is not associated with VHL disease.[5]

# PATIENT GROUP

## DISEASE BACKGROUND

VHL disease is an autosomal dominant genetic condition that arises from a deletion or mutation in the VHL gene. The normal VHL gene acts as a tumour-suppressor gene with the function of preventing the formation of tumours by regulating cellular hypoxia signalling via its product the VHL protein (pVHL).[6] In the case of a non-functioning gene such as in VHL, the loss of the pVHL results in accumulation of HIF-α inside the tumour cell which dimerizes with HIF-β.[6,7] This HIF complex transcriptionally activates genes promoting the adaptation to hypoxia that is implicated in tumour development.[7] This results in increased levels of the various growth factors allowing for increased blood vessel growth and formation of tumours.[6]

People with VHL have an increased risk of developing ccRCC.[8] ccRCC is the most common type of kidney cancer, comprising 75% of all kidney tumours.[9] In renal cell cancer (RCC), the cancerous cells start in the lining of the tubules which help to filter blood and make urine.[10] ccRCC is named as such because when the tumour is viewed under the microscope, the cells in the tumour look clear.[11] Renal cell carcinomas are asymptomatic in the early stages. Patients become symptomatic when the tumour has reached a late stage and/or metastases are present. Haematuria is the most common presenting symptom, other symptoms include anaemia, dragging/colicky flank pain, palpable renal mass, weight loss, fatigue, night sweats and fever.[12]

## CLINICAL NEED AND BURDEN OF DISEASE

Prevalence of VHL in the EU is estimated to be approximately 0.3 per 10,000 people. Based on the current UK population estimate this would equate to an approximate UK prevalence of 2,004 people.[3,13] Men and women are equally affected and the mean age at diagnosis is 26 years but this can range from infancy up to the 7$^{th}$ decade of life.[14] RCCs are found in 24% to 45% of patients with VHL and are the primary inherited renal cancer, they are always of the clear cell type.[15,16] The mean age of RCC onset in VHL patients is 39 years old, which is 25 years less than the mean age of the typical patient.[15]

In England, in 2019-20, there were 289 finished consultant episodes (FCE) for other phakomatoses, not otherwise classified (ICD-10 code Q85.8 resulting in 272 admissions, 202 day cases and 267 FCE bed days.[17]

The Office of National Statistics reported in 2017 that the overall 1 year age-standardised survival rate for kidney cancer was 79.3% and overall 5 year age-standardised survival rate was 63.8%.[18] VHL alterations have been associated with improved cancer-free survival and cancer-specific survival in patients with stage I-III ccRCC who have undergone nephrectomy.[19]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

Active surveillance is important for anyone living with VHL disease. Active surveillance and appropriate treatment can greatly reduce the most harmful consequences of this gene mutation.[20] Regular screening is advised to detect RCC at an early stage and small tumours are followed with serial imaging. The goal is to treat patients before the tumour metastasizes, but to minimize consequences of the treatment such as compromised renal function. ccRCC

grows slowly and small tumours less than 3cm are at low risk to metastasize in VHL. Active surveillance is recommended until the tumours reach a size of 3-4cm when surgical intervention is then recommended.[21]

Preserving the kidney's function with the intent of preventing or delaying dialysis is an important part of the current surgical approach to VHL associated ccRCC. Surgeons will try to remove kidney tumours whilst trying to leave as much normal kidney behind as possible. This is known as nephron sparing surgery or partial nephrectomy. This is generally done with enucleative resection, taking zero margins as the tumour capsule is separated from surrounding parenchyma.[8]

## CURRENT TREATMENT OPTIONS

Currently there are no therapeutic interventions authorised by in the UK/EU for the treatment of VHL. Current treatment focuses on surgery to remove tumours in the affected organs.[3]

## PLACE OF TECHNOLOGY

If licensed, belzutifan will offer an additional treatment option for patients with VHL disease associated ccRCC.[1]

# CLINICAL TRIAL INFORMATION

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| **Trial** | NCT03401788; EudraCT-2018-000125-30; An open-label Phase 2 Study to evaluate PT2977 for the treatment of Von Hippel Lindau Disease-Associated Renal Cell Carcinoma<br>**Phase II** – Active, not recruiting<br>**Locations**: 3 EU countries (incl UK) and USA<br>**Estimated primary completion date:** 29 March 2022 |
| **Trial design** | Open-label, Single group assignment |
| **Population** | N=50 (estimated enrolment); adults aged 18 years and older; diagnosis of von Hippel Lindau disease, based on a germline VHL alteration; at least 1 measurable solid renal cell carcinoma (RCC) and no RCC tumour that requires immediate surgical intervention |
| **Intervention(s)** | 120mg belzutifan (three 40mg oral tablets taken once daily) |
| **Comparator(s)** | No comparator |
| **Outcome(s)** | Primary outcome measure<br>• Objective response rate (ORR) in VHL disease associated RCC tumours<br>[ Time Frame: Up to approximately 4 years ]<br><br>See trial record for full list of outcome measures |
| **Results (efficacy)** | As of data cut-off, 61 patients were enrolled in the study. Median duration of treatment was 36.1 weeks (range: 0-73), and 95.1% of patients were still on therapy. The results showed a confirmed ORR of 27.9% (n=17) (95% CI: 17.1-40.8); all responses were partial responses, and 43% of patients had stable disease. The median time to response was |

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| | 23.7 weeks (range: 11.6-61.0), and median duration of response was not yet reached (range: 9.1-39.0). Additionally, 86.9% (n=53) of patients had a decrease in size of target lesions.[4] |
| **Results (safety)** | Treatment-related adverse events (TRAEs) occurred in 96.7% of patients with 9.8% being grade 3. There were no grade 4 or 5 TRAEs. The most common all-cause adverse event (≥20%) were anaemia (86.9%), fatigue (57.4%), headache (36.1%), dizziness (31.1%) and nausea (24.6%). Grade 3 all-cause adverse events included fatigue (4.9%), anaemia (3.3%), dyspnoea (1.6%) and weight increase (1.6%).[4] |

# ESTIMATED COST

The estimated cost of belzutifan is not yet known.

# RELEVANT GUIDANCE

## NICE GUIDANCE

- No relevant guidance identified.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a

## OTHER GUIDANCE

- National Organisation for Rare Diseases (NORD). Von Hippel – Lindau Disease. 2019.[6]
- European Society for Medical Oncology (ESMO). Renal Cell Carcinoma: ESMO Clinical Practice Guidelines. 2019.[22]
- West Midlands Expert Advisory Group for Urological Cancer. Guidelines for the Management of Renal Cancer. 2016.[23]

# ADDITIONAL INFORMATION

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