Summary Report of Benefit-Risk Assessment

WELIREG FILM-COATED TABLET 40MG

NEW DRUG APPLICATION

Active Ingredient(s)	Belzutifan
Product Registrant	MSD Pharma (Singapore) Pte. Ltd.
Product Registration Number	SIN17233P
Application Route	Abridged evaluation
Date of Approval	09 May 2025

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A INTRODUCTION

Welireg is indicated for the following:

von Hippel-Lindau (VHL) disease associated tumours
WELIREG is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated localised renal cell carcinoma (RCC), central nervous system (CNS) haemangioblastomas, or pancreatic neuroendocrine tumours (pNET), not requiring immediate surgery.

Advanced Renal Cell Carcinoma (RCC)
WELIREG is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor (VEGF) targeted therapy.

The active substance, belzutifan, is an inhibitor of hypoxia-inducible factor-2α (HIF-2α), which is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilisation and accumulation of HIF-2α. Upon stabilisation, HIF-2α translocates into the nucleus and interacts with HIF-1β to form a transcriptional complex that regulates expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumour growth. Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α-HIF-1β interaction, leading to reduced transcription and expression of HIF-2α target genes.

Welireg is available as film-coated tablets containing 40 mg of belzutifan. Other ingredients in the tablet core are croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide. Ingredients in the film coating include FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol-part hydrolyzed, talc, titanium dioxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, belzutifan, is manufactured at Changzhou SynTheAll Pharmaceutical Co., Ltd, Changzhou, China. The drug product, Welireg, is manufactured at MSD International GmbH, Ballydine, Ireland.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits were appropriately qualified. The analytical methods used were

adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 25ºC with a re-test period of 36 months. The packaging is double low-density polyethylene (LDPE) bags stored in high-density polyethylene (HDPE) drums or alternate container that provides equivalent or better protection.

Drug product:

The tablets are manufactured using a spray-dried dispersion of the drug substance, followed by dry blending, roller compaction, compression and film coating.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 48 months when stored at or below 30ºC. The container closure system is aluminum/aluminum blisters with a pack size of 90 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

VHL

The clinical efficacy of belzutifan in the treatment of adult patients with VHL disease who require therapy for associated localised RCC, CNS haemangioblastomas or pNET was based on data from one pivotal, ongoing, Phase 2, multicentre, open-label, non-randomised, non-comparative study (Study 004) evaluating belzutifan monotherapy in patients with VHL disease who had at least one measurable RCC tumour. Patients may have VHL disease-associated tumours in other organ systems. The study excluded patients with any evidence of metastatic disease and patients who had prior systemic treatments for VHL disease-associated RCC.

Patients received belzutifan 120 mg once daily until progression of disease or unacceptable toxicity. Patients were evaluated radiologically approximately 12 weeks after initiation of treatment and every 12 weeks thereafter.

The single-arm, non-comparative study design is a major limitation of the dataset, as it would be difficult to interpret the clinical relevance of the study results without a comparator arm. Nevertheless, considering the rarity of the disease condition rendering a randomised Phase 3 trial unfeasible, and the lack of systemic treatment options for patients with VHL disease-

associated tumours, the non-comparative study design could be accepted depending on the magnitude of response.

The primary efficacy endpoint was overall response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 as assessed by an independent review committee (IRC). Response assessments were to be confirmed by a second assessment at least 4 weeks after the initial response was documented. The secondary endpoints included duration of response (DOR), time to response (TTR), progression-free survival (PFS), and time to surgery (TTS). The primary efficacy analysis was conducted in the overall study population with VHL-RCC. In addition, efficacy was also evaluated in patients with VHL disease-associated non-RCC tumours. There were no formal statistical hypothesis testing and efficacy results were presented descriptively.

A total of 61 patients were allocated to receive study treatment and were included in the efficacy and safety analysis sets. As of the data cut-off date (01 April 2022), the median duration of follow-up was 37.7 months (range 4.2 to 46.1).

The baseline demographic and disease characteristics of the study population were generally representative of patients diagnosed with VHL-RCC. The median age was 41.0 years (range 19 to 66 years). The majority of patients were White (90.2%) and approximately half were male (52.5%). The majority of patients had VHL Type 1 subtype (83.6%), 3.3% had VHL Type 2A, and 9.8% had Type 2B. All patients had VHL-RCC tumours at baseline as per the inclusion criteria. The most common concurrent non-RCC tumour types were pancreatic lesions (100%), of which 36.1% were pNET, CNS haemangioblastomas (82.0%), and retinal haemangioblastomas (19.7%). Almost all patients (96.7%) had prior VHL-related surgeries, and 77.1% of patients had prior surgical procedures for RCC. The median number of prior surgeries per subject was 5 (range 1 to 15).

Overview of efficacy results (Study 004)

	Belzutifan (N=61)
Primary endpoint	
ORR per IRC	
ORR (CR+PR), n (%) (95% CI)	39 (63.9%) (50.6, 75.8)
Best overall response, n (%) Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD) Not evaluable (NE)	 4 (6.6%) 35 (57.4%) 21 (34.4%) 0 1 (1.6%)
Secondary endpoints	
DOR	
Median (95% CI) (months) Min, Max	NE (NE, NE) 5.4+, 35.8+
TTR	
Median (months) Min, Max	11.1 2.7, 30.5
PFS	
Median (95% CI) (months)	39.2 (38.5, NE)
TTS	
Number of subjects who underwent surgeries, n (%) Median (95% CI) (months)	7 (11.5%) NE (NE, NE)

NE = not estimable

Belzutifan demonstrated an ORR per IRC of 63.9% (95% CI 50.6, 75.8) in patients with VHL-RCC, with 4 patients (6.6%) having a CR and 35 patients (57.4%) having a PR.

The median DOR was not reached (range 5.4+, 35.8+ months) as of the data cut-off date. The TTR was relatively long, with a median TTR of 11.1 months (range 2.7 to 30.5). The median PFS was 39.2 months (95% CI: 38.5, NE). The PFS rate at 36 months was 86.3%. The median TTS was not reached.

The efficacy results in the subgroups of patients with pNET tumours and CNS haemangioblastomas are summarised in the table below.

	Patients with evaluable pNET tumours (N=22)	**Patients with evaluable CNS haemangioblastomas (N=50)**
ORR per IRC, n (%) (95% CI)	20 (90.9%) (70.8, 98.9)	22 (44.0%) (30.0, 58.7)
Best overall response, n (%) CR PR SD PD NE	 7 (31.8%) 13 (59.1%) 2 (9.1%) 0 0	 4 (8.0%) 18 (36.0%) 23 (46.0%) 3 (6.0%) 2 (4.0%)
DOR (months) Median (95% CI) Min, Max	 NE (NE, NE) 11.0+, 37.3+	 NE (30.9, NE) 3.7+, 38.7+
TTR (months) Median Min, Max	 8.2 2.5, 16.4	 5.4 2.3, 33.1
PFS (months) Median (95% CI)	 NE (NE, NE)	 NE (38.4, NE)

NE = not estimable

To contextualise the results from the single-arm, non-comparative pivotal study (Study 004), a Natural History Study was conducted to provide real-world evidence in patients with VHL-RCC. This was a retrospective, non-interventional study of patients with VHL-associated RCC who underwent active surveillance in the absence of systemic therapy, using data registered by the National Cancer Institute (NCI) in a hereditary database. The study population consisted of patients treated at the NCI with confirmed VHL disease and at least one renal solid tumour with available measurements during the study period from 31 July 2004 through 30 June 2020. In a subset of 168 patients that closely matched those of Study 004 and who had at least 3 scans during the assessment window, the real-world confirmed ORR per IRC was 1.79% (95% CI: 0.37, 5.13), with none having a CR and 1.8% having a PR. This data indicates that there is a low likelihood of spontaneous regression of VHL renal tumours.

Despite the limitation of the pivotal study (Study 004) as a single-arm, non-comparative trial, in view of the magnitude of the ORR that was clinically meaningful and durable, and considerably higher than that observed in a real-world population without systemic treatments, the evidence of efficacy of belzutifan for the treatment of patients with VHL disease-associated RCC, pNET and CNS haemangioblastomas was deemed to be adequate.

A Phase 2 study (Study 015 Cohort B1) is ongoing to evaluate the efficacy of belzutifan in patients with VHL disease-associated non-RCC tumours. The company is required to submit the results of this study, as well as the final study report of Study 004, to confirm the efficacy of belzutifan in patients with VHL disease-associated localised tumours.

RCC

The use of belzutifan for the treatment of adult patients with advanced RCC following a PD-1/PD-L1 inhibitor and a VEGF targeted therapy was supported by one pivotal Phase 3, multicentre, open-label, randomised study (Study 005) of belzutifan compared to everolimus in patients with unresectable, locally advanced or metastatic clear cell RCC (ccRCC) who had disease progression on or after having received systemic treatment for locally advanced or metastatic RCC with both a PD-1/PD-L1 checkpoint inhibitor and a VEGF targeted therapy. Patients were to have received no more than 3 prior systemic regimens for locally advanced or metastatic RCC.

Patients were randomised 1:1 to receive either belzutifan 120 mg once daily or everolimus 10 mg once daily. Randomisation was stratified by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic scores (favourable vs intermediate vs poor) and number of prior VEGF targeted therapies for advanced RCC (1 vs 2-3). Treatment continued until disease progression or unacceptable adverse events. Patients were evaluated radiologically at Week 9, then every 8 weeks thereafter for the first 49 weeks, and then every 12 weeks thereafter. The use of everolimus in this disease setting was in accordance with clinical practice guidelines and is considered an acceptable active comparator.

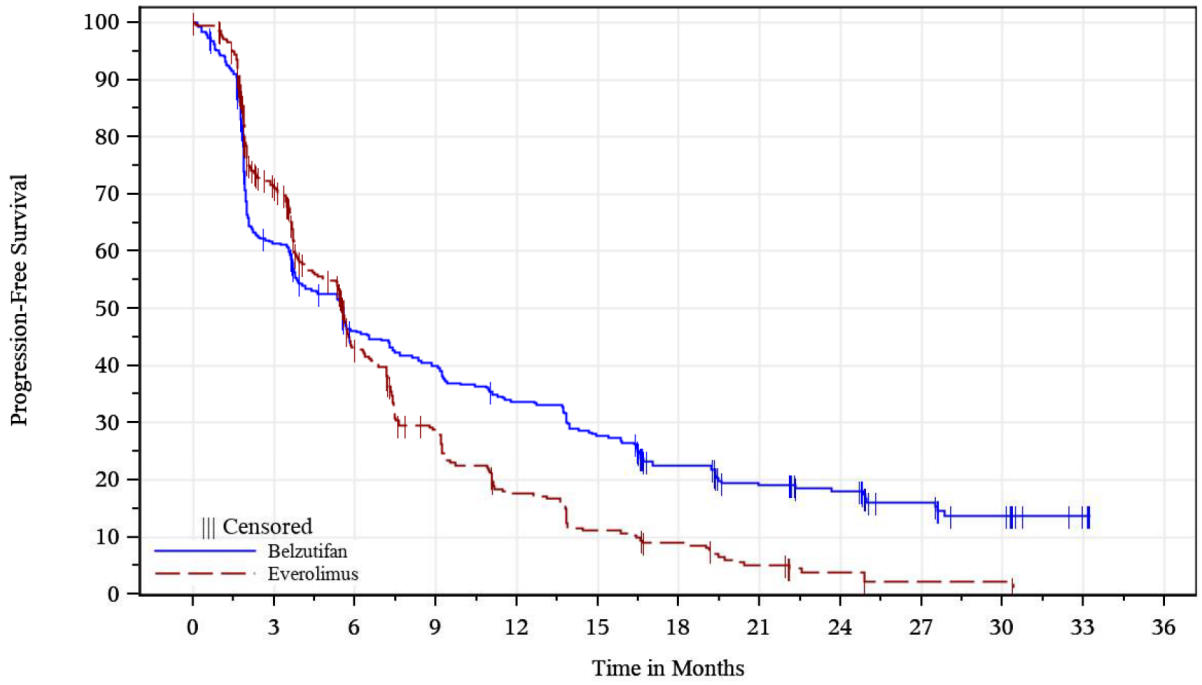
The co-primary efficacy endpoints were PFS (defined as the time from randomisation to the first documented disease progression or death due to any cause, whichever occurred first) per RECIST 1.1 as assessed by blinded independent central review (BICR), and overall survival (OS; defined as the time from randomisation to death due to any cause). The secondary endpoints included ORR and DOR. Appropriate statistical methods were used and multiplicity adjustments were applied for the multiple endpoints and interim analyses planned.

A total of 746 patients were randomised in the study and included in the intent-to-treat (ITT) population: 374 patients in the belzutifan group and 372 in the everolimus group. The patient demographics and baseline characteristics were generally well balanced between the two treatment groups. The majority of patients were male (77.9%) and White (78.8%), and 12.1% were Asian. The median age was 63.0 years (range 22 to 90 years), and 42.0% were aged ≥65 years. Patient distribution by IMDC risk categories was 21.7% favourable, 66.1% intermediate, and 12.2% poor. Most of the patients had received 2 (43.3%) or 3 (42.8%) prior lines of therapy, and 13.1% had received 1 prior line of therapy. All patients had received prior PD-1/PD-L1 and VEGF targeted therapies alone or in combination, as per the study inclusion criteria. Almost half of the patients (49.5%) had received 2 to 3 prior VEGF targeted therapies. The recruited population in the study was overall representative of a patient population with previously treated advanced RCC.

At interim analysis 1 (IA1; data cut-off 01 November 2022), with a median duration of follow-up of 13.5 months (range 0.2, 31.8), belzutifan showed a statistically significant improvement in PFS per BICR compared to everolimus (HR 0.75; 95% CI: 0.63, 0.90; one-sided p=0.00077, which crossed the pre-specified boundary for statistical significance of 0.0021). The median PFS was similar between the belzutifan group (5.6 months) and the everolimus group (5.6 months). The confirmed ORR per BICR was significantly higher in the belzutifan group compared to the everolimus group (21.9% vs 3.5%; one-sided p<0.00001, which crossed the pre-specified boundary for statistical significance of 0.001). However, the OS was not statistically significant (HR 0.87; 95% CI: 0.71, 1.07; one-sided p=0.09583, which did not cross the statistical boundary of 0.0045), although the median OS numerically favoured belzutifan over everolimus (21.0 vs 17.2 months).

At interim analysis 2 (IA2; data cut-off 13 June 2023), the median duration of follow-up was 17.8 months (range 0.2, 39.1). The PFS results continued to show improvement in the belzutifan group over everolimus (HR 0.74; 95% CI: 0.63, 0.88; one-sided nominal p=0.00031), although the median PFS remained similar between the treatment groups (5.6 months). The proportion of PFS events was numerically higher in the belzutifan group compared to the everolimus group (77.3% vs 74.2%). From the Kaplan-Meier plot of PFS, the curves during the first 6 months appeared to favour everolimus, before crossing and separating at approximately 6 months and remained separated thereafter in favour of belzutifan. This suggested that the treatment benefits of belzutifan over everolimus became apparent only after 6 months of treatment.

Kaplan-Meier plot of PFS per BICR (ITT population; IA2)



At Risk

Belzutifan	374	218	156	135	113	93	66	45	35	21	14	4	0
Everolimus	372	226	113	70	41	26	19	10	5	2	2	0	0

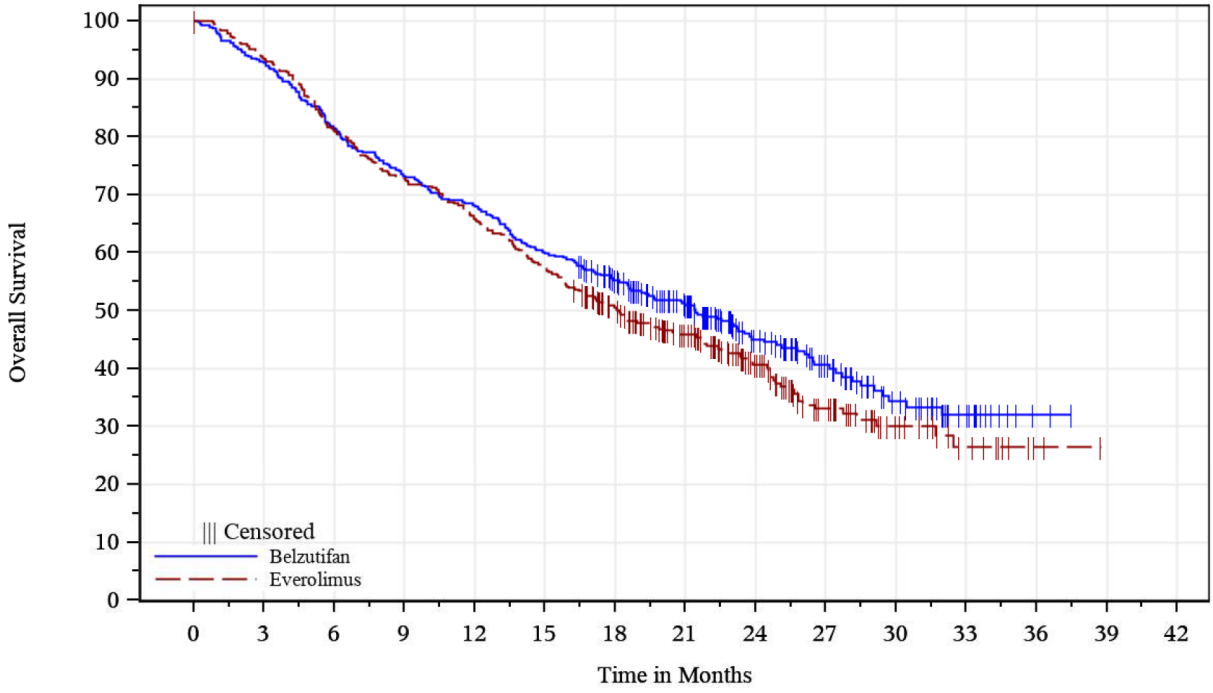
The higher proportion of PFS events in the belzutifan group and early pattern of the PFS curves could be contributed by higher early censoring in the everolimus group for new anticancer therapy compared to the belzutifan group. At the time of the IA2 cut-off date, 25 patients in the belzutifan group and 79 in the everolimus group were censored within 6 months for PFS primary analysis. The main reason for early censoring was new anticancer therapy (20 in the belzutifan group vs 69 in the everolimus group). Pre-specified sensitivity analyses of PFS performed using different censoring rules to account for initiation of new anticancer therapy showed lower percentage of PFS events in the belzutifan group (82.6% to 85.0%) versus the everolimus group (87.4% to 98.1%) and comparable HRs (0.69 to 0.74) with that of the primary analysis.

Consistent PFS results were also demonstrated in pre-specified subgroup analyses, including in patients with 1, 2 or 3 prior lines of therapy (HR 0.54, 0.81 and 0.77, respectively) and

regardless of IMDC risk categories (HR 0.74 for favourable; 0.75 for intermediate and 0.67 for poor).

The results for OS at IA2 were consistent with that at IA1. The OS HR was 0.88 (95% CI: 0.73, 1.07; one-sided p=0.09941), which was not statistically significant as the p-value did not cross the statistical boundary for significance of 0.014. The median OS was 21.4 months (95% CI: 18.2, 24.3) in the belzutifan group and 18.1 months (95% CI: 15.8, 21.8) in the everolimus group.

Kaplan-Meier plot of OS (ITT population; IA2)



At Risk

Belzutifan	374	347	305	274	254	224	190	143	95	62	36	16	2	0	0
Everolimus	372	347	301	270	244	212	170	124	83	43	23	11	2	0	0

The confirmed ORR per BICR at IA2 was 22.7% (95% CI: 18.6, 27.3) in the belzutifan group and 3.5% (95% CI: 1.9, 5.9) in the everolimus group, with an estimated treatment difference of 19.2% (95% CI: 14.8, 24.0; one-sided nominal p<0.00001). The median DOR was 19.5 months (range 1.9+ to 31.6+ months) for the belzutifan group and 13.7 months (range 3.8 to 21.2+ months) for the everolimus group.

Updated data from the final analysis with a median follow-up time of 19.6 months (data cut-off date 15 April 2024) showed consistent results with that of IA1 and IA2. The results of IA1, IA2 and the final analysis are summarised in the table below.

Overview of efficacy results (Study 005)

	IA1 (cut-off date 01 Nov 2022)		IA2 (cut-off date 13 Jun 2023)		Final analysis (cut-off date 15 Apr 2024)	
	Belzutifan (N=374)	**Everolimus (N=372)**	**Belzutifan (N=374)**	**Everolimus (N=372)**	**Belzutifan (N=374)**	**Everolimus (N=372)**
Primary endpoints						
PFS per BICR						
Number of events (%)	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)	308 (82.4%)	279 (75.0%)
Median (months) (95% CI)	5.6 (3.9, 7.0)	5.6 (4.8, 5.8)	5.6 (3.8, 6.5)	5.6 (4.8, 5.8)	5.6 (3.8, 6.5)	5.6 (4.8, 5.8)
HR (95% CI)[a]	0.75 (0.63, 0.90)		0.74 (0.63, 0.88)		0.75 (0.63, 0.88)	
p-value[b]	0.00077		0.00031[e]		0.00034[e]	
OS						
Number of events (%)	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)	254 (67.9%)	259 (69.6%)
Median (months) (95% CI)	21.0 (17.2, 24.3)	17.2 (15.3, 19.0)	21.4 (18.2, 24.3)	18.1 (15.8, 21.8)	21.4 (18.2, 24.3)	18.2 (15.8, 21.8)
HR (95% CI)[a]	0.87 (0.71, 1.07)		0.88 (0.73, 1.07)		0.92 (0.77, 1.10)	
p-value[b]	0.09583		0.09941		0.17644	
Secondary endpoints						
ORR						
Best objective response, n (%)						
CR	10 (2.7%)	0 (0.0%)	13 (3.5%)	0 (0.0%)	-	-
PR	72 (19.3%)	13 (3.5%)	72 (19.3%)	13 (3.5%)		
SD	147 (39.3%)	245 (65.9%)	143 (38.2%)	245 (65.9%)		
PD	126 (33.7%)	80 (21.5%)	127 (34.0%)	80 (21.5%)		
Not evaluable	5 (1.3%)	8 (2.2%)	5 (1.3%)	8 (2.2%)		
No assessment	14 (3.7%)	26 (7.0%)	14 (3.7%)	26 (7.0%)		
ORR (CR+PR), n (%) (95% CI)	82 (21.9%) (17.8, 26.5)	13 (3.5%) (1.9, 5.9)	85 (22.7%) (18.6, 27.3)	13 (3.5%) (1.9, 5.9)	85 (22.7%) (18.6, 27.3)	13 (3.5%) (1.9, 5.9)
Treatment difference (95% CI)[c]	18.4 (14.0, 23.2)		19.2 (14.8, 24.0)		19.2 (14.8, 24.1)	
p-value[d]	<0.00001		<0.00001[e]		<0.00001[e]	
DOR						
Median (months) (range)	NR (1.7+, 23.2+)	17.2 (3.8, 18.0+)	19.5 (1.9+, 31.6+)	13.7 (3.8, 21.2+)	-	-

NR = not reached; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

[a] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by IMDC risk group (favourable vs intermediate vs poor) and number of prior VEGF targeted therapies for advanced RCC (1 vs 2-3).

[b] One-sided p-value based on log-rank test stratified by IMDC risk group (favourable vs intermediate vs poor) and number of prior VEGF targeted therapies for advanced RCC (1 vs 2-3).

[c] Based on Miettinen & Nurminen method stratified by IMDC risk group (favourable vs intermediate vs poor) and number of prior VEGF targeted therapies for advanced RCC (1 vs 2-3).

[d] One-sided p-value.

[e] Statistical significance for PFS and ORR were demonstrated at IA1, hence the results for PFS and ORR at IA2 and final analysis were presented descriptively with nominal p-values.

Overall, the efficacy of belzutifan was adequately demonstrated based on statistically significant improvements over everolimus in terms of PFS and ORR and supported by numerically longer DOR and a trend towards improvement in OS in patients with advanced RCC who had progressed on prior PD-1/PD-L1 and VEGF targeted therapies.

D ASSESSMENT OF CLINICAL SAFETY

VHL

The safety assessment of belzutifan in the treatment of VHL disease associated tumours was based primarily on safety data from the pivotal Phase 2 study (Study 004) in 61 patients with VHL disease-associated RCC treated with belzutifan 120 mg once daily. As of the data cut-off date of 01 April 2022, the median duration of exposure was 37.3 months (range 1.94 to 46.06).

Adverse event (AE) summary (Study 004)

	Belzutifan (N=61)
Any AE	61 (100.0%)
Treatment-related AE	61 (100.0%)
Grade ≥3 AE	27 (44.3%)
Serious AE (SAE)	18 (29.5%)
Treatment-related SAE	4 (6.6%)
Treatment discontinuation due to AE	4 (6.6%)
Dose modification[a] due to AE	32 (52.5%)
Dose interruption due to AE	26 (42.6%)
Dose reduction due to AE	10 (16.4%)
Death due to AE	2 (3.3%)
Death due to treatment-related AE	0 (0.0%)

[a] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

The most frequently reported AEs with belzutifan were anaemia (90.2%), fatigue (73.8%), headache (47.5%), dizziness (45.9%), nausea (39.3%), dyspnoea (26.2%), myalgia (24.6%), constipation (23.0%), arthralgia (21.3%), and vision blurred (21.3%). The most frequently reported treatment-related AEs were anaemia (88.5%), fatigue (63.9%), dizziness (24.6%), and nausea (24.6%). The most common Grade ≥3 AEs were anaemia (11.5%) and hypertension (9.8%).

A total of 29.5% of subjects reported SAEs, of which haemorrhage intracranial and embolism (each reported by 2 subjects [3.3%]) were the only events reported by more than 1 subject. There were 6.6% of subjects who discontinued study treatment due to AEs, including dizziness and haemorrhage intracranial which were assessed as treatment-related in 1 subject each. There were no treatment-related fatal AEs reported in the study.

Based on a review of the totality of safety data from the belzutifan clinical program, events of anaemia and hypoxia were identified as the most clinically important adverse drug reactions. Anaemia was the most frequently reported AE in Study 004 (55 [90.2%] subjects) and almost all anaemia events (54 [88.5%] subjects) were assessed as treatment-related. There were no treatment discontinuations due to anaemia. Most patients did not require dose modification for anaemia events: 2 (3.3%) patients had a dose interruption and 2 (3.3%) had a dose reduction for anaemia. Among the 55 patients with anaemia, 15 were treated with erythropoiesis-stimulating agents (ESA) and/or blood transfusion.

Hypoxia was reported in 1 (1.6%) subject in Study 004, 56 days after starting study treatment. The event was Grade 3 in severity and was assessed as related to study treatment. The event was managed through dose reduction to 80 mg once daily and no supplemental oxygen was required, and the event resolved after 51 days.

The safety profile of belzutifan was overall deemed to be acceptable in patients with VHL-associated tumours. The key toxicities, mainly anaemia and hypoxia, have been detailed in

the package insert with appropriate warnings, and can be managed with monitoring, dose modifications and supportive therapy.

RCC

The safety of belzutifan in the treatment of patients with advanced RCC was evaluated based on data from the pivotal Phase 3 study (Study 005) in 732 patients with advanced RCC treated with belzutifan 120 mg once daily (n=372) or everolimus 10 mg once daily (n=360). As of the data cut-off date (13 June 2023), the median duration of exposure was 7.6 months (range 0.10 to 35.84) in the belzutifan group and 3.9 months (range 0.03 to 33.25) in the everolimus group.

In addition, safety data was pooled from the two pivotal VHL and RCC studies (Studies 004 and 005), a Phase 1, first-in-human, dose-finding study (Study 001) in patients with advanced solid tumours, as well as a Phase 2, randomised, open-label study (Study 013) in patients with advanced RCC previously treated with anti-PD-1/PD-L1 therapy, providing supportive safety data in a total of 576 patients treated with belzutifan 120 mg once daily. The median duration of exposure in the pooled safety dataset was 9.2 months (range 0.10 to 55.43).

Summary of AEs

	Study 005		Pooled dataset
	Belzutifan (N=372)	**Everolimus (N=360)**	**Belzutifan (N=576)**
Any AE	369 (99.2%)	357 (99.2%)	572 (99.3%)
Treatment-related AE	331 (89.0%)	322 (89.4%)	526 (91.3%)
Grade ≥3 AE	230 (61.8%)	225 (62.5%)	355 (61.6%)
SAE	157 (42.2%)	137 (38.1%)	236 (41.0%)
Treatment-related SAE	49 (13.2%)	47 (13.1%)	71 (12.3%)
Treatment discontinuation due to AE	22 (5.9%)	53 (14.7%)	37 (6.4%)
Dose modification[a] due to AE	191 (51.3%)	225 (62.5%)	288 (50.0%)
Dose interruption due to AE	162 (43.5%)	173 (48.1%)	235 (40.8%)
Dose reduction due to AE	52 (14.0%)	53 (14.7%)	89 (15.5%)
Death due to AE	13 (3.5%)	19 (5.3%)	19 (3.3%)
Death due to treatment-related AE	1 (0.3%)	2 (0.6%)	1 (0.2%)

[a] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

In Study 005, the most frequently reported AEs in the belzutifan group and their incidences (belzutifan vs everolius) included anaemia (82.8% vs 56.7%), fatigue (31.5% vs 25.3%), nausea (18.0% vs 11.4%), constipation (16.7% vs 8.1%), oedema peripheral (16.1% vs 16.9%), dyspnoea (15.1% vs 14.2%), back pain (14.8% vs 8.3%), arthralgia (14.5% vs 7.5%), asthenia (14.5% vs 16.9%), decreased appetite (14.5% vs 15.8%), hypoxia (14.5% vs 1.1%), vomiting (12.9% vs 8.9%), dizziness (12.4% vs 1.7%), alanine aminotransferase (ALT) increased (12.1% vs 8.9%), headache (12.1% vs 7.5%), diarrhoea (11.8% vs 19.7%), and aspartate aminotransferase (AST) increased (11.6% vs 8.9%).

The AEs that were reported with higher incidence in the belzutifan group than in the everolimus group were anaemia, fatigue, nausea, constipation, back pain, arthralgia, hypoxia, and dizziness. Treatment-related AEs reported more frequently with belzutifan compared to everolimus were anaemia (71.8% vs 34.2%), fatigue (21.2% vs 16.7%), and hypoxia (11.8% vs 0.0%).

The AEs reported with higher incidence in the everolimus group included stomatitis (37.8% in the everolimus group vs 3.5% in the belzutifan group), cough (20.6% vs 8.3%), diarrhoea (19.7% vs 11.8%), rash (18.9% vs 4.6%), pruritus (16.7% vs 7.8%), hyperglycaemia (15.0%

vs 2.7%), hypertriglyceridaemia (14.7% vs 3.8%), pneumonitis (14.2% vs 0.8%), and pyrexia (12.8% vs 5.9%).

The proportion of patients who reported Grade ≥3 AEs was similar between the belzutifan and everolimus groups (61.8% vs 62.5%). The most common Grade ≥3 AEs were anaemia (32.5% vs 18.1%) and hypoxia (10.5% vs 1.1%).

SAEs were reported in 42.2% of patients in the belzutifan group and 38.1% in the everolimus group. The most frequently reported SAEs were hypoxia (7.5% vs 0.0%), anaemia (5.4% vs 2.2%), and pneumonia (4.6% vs 4.7%). The incidence of AEs leading to treatment discontinuation was lower in the belzutifan group than in the everolimus group (5.9% vs 14.7%). The only AE leading to treatment discontinuation reported in more than 1 subject in the belzutifan group was hypoxia (3 subjects [0.8%]), all assessed as treatment-related.

The incidence of AEs leading to death was similar in both treatment groups (3.5% in the belzutifan group vs 5.3% in the everolimus group). All fatal AEs in the belzutifan group were reported in one patient each. One fatal AE in the belzutifan group (multiple organ dysfunction syndrome) was assessed by the investigator as related to study drug. In the everolimus group, fatal AEs of sepsis and acute kidney injury were assessed as treatment-related.

The clinically important adverse drug reactions associated with belzutifan treatment were anaemia and hypoxia. Anaemia (as a grouped term comprising AEs of anaemia and haemoglobin decreased) was reported by 83.1% of patients in the belzutifan group and 56.9% in the everolimus group. The majority were assessed as treatment-related events (72.0% vs 34.4%). There were few treatment discontinuations (0.3% vs 0.6%) required for anaemia, and dose modifications were required in 11.6% of patients in the belzutifan group and 3.6% in the everolimus group. Among the patients with anaemia in the belzutifan group, 20.1% were treated with ESAs only, 21.7% received blood transfusion only, and 13.6% received both an ESA and blood transfusion.

Hypoxia was reported in 14.5% of patients in the belzutifan group and 1.1% in the everolimus group. The majority of hypoxia AEs in the belzutifan group were assessed as treatment-related (11.8%). Three patients (0.8%) in the belzutifan group discontinued treatment due to hypoxia and 10.5% of patients required dose modification. Of the patients who had hypoxia in the belzutifan group, 70.4% were treated with supplemental oxygen.

The safety profile of belzutifan was generally consistent with that documented in patients with VHL and considered acceptable in the target patient population with advanced RCC. Clinically important events of anaemia and hypoxia can be managed with dose modifications and/or treatment with ESAs/blood transfusions for anaemia or supplemental oxygen for hypoxia. Adequate warnings on anaemia and hypoxia have been included in the package insert, including recommendations for periodic monitoring and dose modifications in the event of Grade ≥3 anaemia or hypoxia.

E ASSESSMENT OF BENEFIT-RISK PROFILE

VHL

VHL disease is a rare, serious and potentially life-threatening condition. Patients with VHL disease are at risk for developing tumours affecting various organs, including RCC, CNS

haemangioblastoma, and pNET. Management of the disease involves lifelong surveillance and multiple surgical procedures, which are associated with substantial morbidity and are not curative. There is no approved systemic therapy for the treatment of VHL disease-associated tumours, representing an unmet medical need for this population.

The pivotal Phase 2 study (Study 004) has shown promising results in patients with VHL-RCC, with a clinically meaningful ORR per IRC of 63.9% (95% CI: 50.6, 75.8), including 6.6% having a CR. The responses were shown to be durable, with the median DOR not reached after a median follow-up time of 37.7 months. Responses were also seen in other VHL-associated non-RCC tumours, including an ORR of 90.9% (95% CI: 70.8, 98.9) in patients with pNET and 44.0% (95% CI: 30.0, 58.7) in patients with CNS haemangioblastomas.

The safety profile of belzutifan is acceptable, with most AEs managed by dose interruption or reduction and few requiring treatment discontinuations (6.6%). The most common AEs were anaemia (90.2%), fatigue (73.8%), headache (47.5%), dizziness (45.9%), nausea (39.3%), dyspnoea (26.2%), myalgia (24.6%), constipation (23.0%), arthralgia (21.3%), and vision blurred (21.3%). Anaemia and hypoxia are the most clinically important adverse drug reactions identified for belzutifan. Appropriate warnings have been included in the package insert, including management of anaemia with ESAs/blood transfusions and with supplemental oxygen for hypoxia, as well as recommendations for monitoring and dose modifications.

Taking into consideration the good and durable response rates demonstrated with belzutifan treatment and the manageable safety profile, the benefit-risk profile of belzutifan for the treatment of adult patients with VHL disease who require therapy for associated RCC, CNS haemangioblastomas or pNET but not requiring immediate surgery is considered favourable.

RCC

Advanced RCC is a serious and life-threatening disease, with a 5-year survival rate of approximately 14%. There is currently no standard of care approved for patients with advanced RCC whose disease has progressed following treatment with anti-PD-1/PD-L1 and VEGF targeted therapies. Therefore, there continues to be a need for safe and effective treatment options for the management of patients in this setting.

The Phase 3 Study 005 showed a modest but statistically significant improvement in PFS per BICR for belzutifan compared to everolimus, with a PFS HR of 0.75 (95% CI: 0.63, 0.90; one-sided p=0.00077) at IA1, which was supported by consistent results at IA2 and the final analysis. The confirmed ORR per BICR was significantly higher with belzutifan vs everolimus at IA1 (21.9% vs 3.5%; one-sided p<0.00001), which was also consistent at both IA2 and the final analysis. The median DOR at IA2 was numerically longer with belzutifan compared to everolimus (19.5 vs 13.7 months). The OS, although not statistically significant, numerically favoured belzutifan (IA2: median 21.4 vs 18.1 months; HR 0.88; 95% CI: 0.73, 1.07; one-sided p=0.09941; final analysis: median 21.4 vs 18.2 months; HR 0.92; 95% CI: 0.77, 1.10; one-sided p=0.17644).

The proportion of patients with AEs (99.2% vs 99.2%), including Grade ≥3 AEs (61.8% vs 62.5%), SAEs (42.2% vs 38.1%) and fatal AEs (3.5% vs 5.3%) were comparable between belzutifan and everolimus, while the incidence of AEs leading to dose modification (51.3% vs 62.5%) and AEs leading to treatment discontinuation (5.9% vs 14.7%) were lower with belzutifan compared to everolimus. The AEs with higher incidence in the belzutifan group compared to everolimus were anaemia (82.8% vs 56.7%), fatigue (31.5% vs 25.3%), nausea (18.0% vs 11.4%), constipation (16.7% vs 8.1%), back pain (14.8% vs 8.3%), arthralgia (14.5%

vs 7.5%), hypoxia (14.5% vs 1.1%), and dizziness (12.4% vs 1.7%). Anaemia (32.5% vs 18.1%) and hypoxia (10.5% vs 1.1%) were the most common Grade ≥3 AEs reported with belzutifan, and these important toxicities have been adequately described in the package insert. Belzutifan has a safety profile that is distinct from everolimus and other VEGF targeted therapies, and could present an alternative treatment option for the target patient population.

Overall, based on the benefits demonstrated in terms of PFS and ORR for belzutifan over everolimus and the acceptable safety profile that was consistent with that in patients with VHL disease, the benefit-risk balance of belzutifan for the treatment of adult patients with advanced RCC following a PD-1/PD-L1 inhibitor and a VEGF targeted therapy is considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Welireg for the treatment of adult patients with VHL disease who require therapy for associated localised RCC, CNS haemangioblastomas or pNET but not requiring immediate surgery, and for the treatment of adult patients with advanced RCC following a PD-1/PD-L1 inhibitor and a VEGF targeted therapy, is deemed favourable and approval of the product registration was granted on 09 May 2025.

The approval is subject to the submission of the final study reports of Study 015 (Cohort B1) and Study 004 to confirm the clinical benefit and favourable overall benefit-risk profile of belzutifan in the treatment of VHL disease-associated tumours.

APPROVED PACKAGE INSERT AT REGISTRATION

WELIREG® (Belzutifan)

Tablet

1. INDICATIONS AND USAGE

1.1 von Hippel-Lindau (VHL) disease associated tumors

WELIREG (belzutifan) is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated localized renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

1.2 Advanced Renal Cell Carcinoma (RCC)

WELIREG is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor (VEGF) targeted therapy.

2. DOSAGE AND ADMINISTRATION

2.1 General

The recommended dose of WELIREG is 120 mg (three 40 mg tablets) administered orally once daily, with or without food. Swallow tablets whole.

If a dose of WELIREG is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for WELIREG the next day. Extra tablets should not be taken to make up for the missed dose. If vomiting occurs any time after taking WELIREG, do not retake the dose. The next dose should be taken the next day. Treatment should continue until disease progression or unacceptable toxicity occurs.

2.2 Dose Modifications

Dosage modifications for WELIREG for adverse reactions are summarized in Table 1.

Table 1: Recommended Dose Modifications

Adverse Reactions	Severity	Dose Modification
Anemia due to decreased erythropoietin *[see 5. WARNINGS AND PRECAUTIONS (5.1)]*	Grade 3	• Withhold until resolved to ≤ Grade 2. • Resume at the same or reduced dose (reduce by 40 mg); consider discontinuing depending on the severity and persistence of anemia.
	Grade 4	• Withhold until resolved to ≤ Grade 2. • Resume at a reduced dose (reduce by 40 mg) or permanently discontinue upon recurrence of Grade 4.
Hypoxia *[see 5. WARNINGS AND PRECAUTIONS (5.2)]*	Grade 3 (asymptomatic)	• Option to continue or withhold until resolved to ≤ Grade 2. • Resume at reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of hypoxia.
	Grade 3 (symptomatic)	• Withhold until resolved to ≤ Grade 2. • Resume at reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of hypoxia.
	Grade 4	• Permanently discontinue.
Other Adverse Reactions *[see 8. ADVERSE REACTIONS]*	Grade 3	• Withhold dosing until resolved to ≤ Grade 2. • Consider resuming at a reduced dose (reduce by 40 mg). • Permanently discontinue upon recurrence of Grade 3.
	Grade 4	• Permanently discontinue.

Based on Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

2.3 Pediatric Patients

Safety and efficacy of WELIREG have not been established in pediatric patients less than 18 years of age *[see 6. USE IN SPECIFIC POPULATIONS, 6.4 Pediatric Use and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

2.4 Geriatric Patients

No dose adjustment of WELIREG is recommended in elderly patients *[see 6. USE IN SPECIFIC POPULATIONS, 6.5 Geriatric Use and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

2.5 Renal Impairment

No dose adjustment of WELIREG is recommended in patients with mild and moderate renal impairment. WELIREG has not been studied in patients with severe renal impairment *[see 6. USE IN SPECIFIC POPULATIONS, 6.6 Renal Impairment and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

2.6 Hepatic Impairment

No dose adjustment of WELIREG is recommended in patients with mild hepatic impairment. WELIREG has not been studied in patients with moderate or severe hepatic impairment *[see 6. USE IN SPECIFIC POPULATIONS, 6.7 Hepatic Impairment and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

3. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

4. WARNINGS AND PRECAUTIONS

4.1 Anemia due to Decreased Erythropoietin

In a clinical trial (LITESPARK-004) with WELIREG for the treatment of patients with VHL disease-associated RCC, anemia was reported in 55 patients (90.2%). Grade 3 anemia occurred in 7 patients (11.5%) *[see 7. ADVERSE REACTIONS]*. Median time to onset of all Grade anemia events was 30 days (range: 1 day to 8.38 months). Of the 14 patients that were treated with an erythropoiesis-stimulating agent (ESA), 5 received treatment with both an ESA and blood transfusions, while 9 received treatment with an ESA alone. The median number of ESA doses administered to patients was 5 (range 1-35). Patients received an ESA based on hemoglobin levels and physician discretion *[see 10. CLINICAL PHARMACOLOGY, 10.3 Pharmacodynamics]*. In LITESPARK-005, a clinical trial with WELIREG for the treatment of patients with advanced RCC, anemia occurred in 83% of patients, 119 patients (32%) had Grade 3 and 2 patients (0.5%) had Grade 4 anemia *[see 7. ADVERSE REACTIONS]*. Median time to onset of anemia was 29 days (range: 1 day to 27 months). Of the

patients with anemia, 67 patients (22%) received transfusions only, 62 patients (20%) of patients received ESAs only and 42 patients (14%) received both transfusion and ESAs. The median number of ESA doses administered to patients was 6.5 (range: 1-87). Patients received an ESA based on hemoglobin levels and physician discretion. In another clinical trial (Study-001) for the treatment of non-VHL disease-associated advanced solid tumors using the same dose of WELIREG, anemia was reported in 44 patients (75.9%). Grade 3 anemia occurred in 16 patients (27.6%).

Monitor for anemia before initiation of and periodically throughout treatment with WELIREG. For patients who develop Grade 3 anemia, withhold WELIREG and treat according to standard medical practice, including erythropoiesis-stimulating agent (ESA) administration and/or transfusion until resolved to ≤ Grade 2; then resume at the same or reduced dose. For recurrent Grade 3 anemia, consider discontinuing WELIREG.

For patients who develop Grade 4 anemia, withhold WELIREG; then resume at a reduced dose or permanently discontinue for recurrent Grade 4 anemia *[see 2. DOSAGE AND ADMINISTRATION, 2.2 Dose Modifications]*.

4.2 Hypoxia

In a clinical trial (LITESPARK-004) with WELIREG for the treatment of patients with VHL disease-associated RCC, Grade 3 hypoxia occurred in 1 patient (1.6%) *[see 7. ADVERSE REACTIONS]*. In LITESPARK-005, a clinical trial with WELIREG for the treatment of patients with advanced RCC, hypoxia occurred in 15% of patients and 38 patients (10%) had Grade 3 hypoxia and 1 patient (0.3%) had Grade 4 hypoxia *[see 7. ADVERSE REACTIONS]*. Of the patients with hypoxia, 70% were treated with oxygen therapy. Median time to onset of hypoxia was 1 month (range: 1 day to 21 months).

In another clinical trial (Study-001) for the treatment of non-VHL disease-associated advanced solid tumors using the same dose of WELIREG, hypoxia occurred in 17 patients (29.3%), Grade 3 hypoxia occurred in 9 patients (15.5%).

Monitor oxygen saturation with pulse oximetry before initiation of and periodically throughout treatment with WELIREG. For Grade 3 asymptomatic hypoxia, consider providing supplemental oxygen and consider continuing or withholding treatment. If withheld, resume at a reduced dose. For patients who have Grade 3 symptomatic hypoxia, withhold WELIREG, treat hypoxia, and consider dose reduction. If symptomatic hypoxia continues to recur, discontinue treatment. For Grade 4

hypoxia, permanently discontinue treatment *[see 2. DOSAGE AND ADMINISTRATION, 2.2 Dose Modifications]*.

4.3 Embryo-Fetal Toxicity

Based on findings in animals, WELIREG may cause fetal harm, including fetal loss, in humans. In a rat study, WELIREG caused embryo-fetal toxicity when administered during the period of organogenesis at maternal exposures that were lower than the human exposures at the recommended dose of 120 mg daily. Advise females of reproductive potential to use highly effective non-hormonal contraceptive methods during treatment with WELIREG and for 1 week after the last dose due to the potential risk to the fetus. Advise males with female partners of reproductive potential to use highly effective contraception during treatment with WELIREG and for 1 week after the last dose *[see 6. USE IN SPECIFIC POPULATIONS, 6.1 Pregnancy, 6.3 Females and Males of Reproductive Potential and 11. ANIMAL TOXICOLOGY, 11.6 Development]*.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

In vitro and pharmacogenomic studies indicate that WELIREG is metabolized by UGT2B17 and by CYP2C19.

5.1 Effects of WELIREG on Other Drugs

Co-administration of WELIREG with CYP3A4 substrates, including hormonal contraceptives, decreases concentrations of CYP3A4 substrates, which may reduce the efficacy of these substrates. The magnitude of this decrease may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolizers *[see 10 CLINICAL PHARMACOLOGY].*

Co-administration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding.

5.2 Effects of Other Drugs on WELIREG

Co-administration with inhibitors of UGT2B17 or CYP2C19 is expected to increase plasma belzutifan exposure, which may increase the incidence and severity of adverse reactions of WELIREG. Monitor for anemia and hypoxia and reduce the dosage of WELIREG as recommended *[see 2. DOSAGE AND ADMINISTRATION and 4. WARNINGS AND PRECAUTIONS]*. Drugs that induce CYP2C19 are expected to reduce plasma exposures of WELIREG.

5.3 Effects on ability to drive and use machines

Dizziness and fatigue may occur following administration of belzutifan *[see 7 ADVERSE REACTIONS]*.

Patients should be advised not to drive and use machines, until they are reasonably certain belzutifan therapy does not affect them adversely.

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

Based on findings in animal studies, WELIREG may cause fetal harm, including fetal loss, when administered to a pregnant woman. There are no available data on the use of WELIREG in pregnant women to evaluate drug-associated risk. In a rat embryo-fetal development study, administration of WELIREG during organogenesis caused embryo-fetal lethality, reduced fetal body weight, and fetal skeletal abnormalities at exposures similar to or below the human exposure at the recommended dose of 120 mg daily. Advise females of reproductive potential of the potential risk to a fetus.

6.2 Nursing Mothers

There are no data on the presence of WELIREG or its metabolites in human milk, their effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with WELIREG and for 1 week after the last dose.

6.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG.

Contraception

WELIREG may cause embryo-fetal harm, including fetal loss, when administered to a pregnant woman *[see 6. USE IN SPECIFIC POPULATIONS, 6.1 Pregnancy]*.

Females

Females of reproductive potential should be advised to use highly effective contraception during treatment with WELIREG and for at least 1 week after last dose. Use of WELIREG may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative non-hormonal contraceptive method or have their male partner use a condom during treatment with WELIREG *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 Effects of WELIREG on Other Drugs]*.

Males

Advise male patients with female partners of reproductive potential to use highly effective contraception during treatment with WELIREG and for at least 1 week after the last dose.

Infertility

Based on findings in animals, WELIREG may impair fertility in males and females of reproductive potential *[see 11. ANIMAL TOXICOLOGY, 11.5 Reproduction]*. Advise patients of this potential risk. The reversibility of the effect on fertility is unknown.

6.4 Pediatric Use

Safety and effectiveness of WELIREG in pediatric patients under 18 years of age have not been established.

6.5 Geriatric Use

No dosage adjustment of WELIREG is recommended in geriatric patients. Of the 61 patients with VHL disease-associated RCC (LITESPARK-004) treated with WELIREG, only 2 patients were 65 years and over. Of the patients with advanced RCC who received WELIREG in LITESPARK-005, 38% (142 patients) were ≥ 65 years old *[see 9. CLINICAL STUDIES]*. Another clinical trial (Study-001) for the treatment of non-VHL disease-associated advanced solid tumors included 24 patients were 65 years and over. No overall difference in safety or efficacy was reported between patients who were 65 years and over and younger patients *[see 9. CLINICAL STUDIES and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

6.6 Renal Impairment

No dose adjustment of WELIREG is recommended in patients with mild or moderate renal impairment. WELIREG has not been studied in patients with severe renal impairment *[see 2. DOSAGE AND ADMINISTRATION, 2.5 Renal Impairment and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

6.7 Hepatic Impairment

No dose adjustment of WELIREG is recommended in patients with mild hepatic impairment. WELIREG has not been studied in patients with moderate or severe hepatic impairment *[see 2. DOSAGE AND ADMINISTRATION, 2.6 Hepatic Impairment and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

6.8 Dual UGT2BI7 and CYP2C19 Poor Metabolizers

Patients who are dual UGT2B17 and CYP2C19 poor metabolizers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of belzutifan and should be closely monitored *[see 4 WARNINGS AND PRECAUTIONS, 4.1 Anemia due to Decreased Erythropoietin, 7. ADVERSE REACTIONS and 10 CLINICAL PHARMACOLOGY]*.

7. ADVERSE REACTIONS

7.1 von Hippel-Lindau (VHL) disease associated tumors

The safety of belzutifan was evaluated in an open-label Phase 2 clinical study (LITESPARK-004), in 61 patients with VHL disease-associated RCC and who did not require immediate surgery. Patients were treated with 120 mg belzutifan once daily. The median duration of exposure to belzutifan was 37.3 months (range 1.9 to 46.1 months).

The most common adverse reactions under treatment with belzutifan were anemia (90%), fatigue (74%), dizziness (46%), nausea (39%), and dyspnea (26%).

The most common adverse reactions resulting in dose interruption of belzutifan were fatigue (11.5%), nausea (9.8%), dizziness (4.9%), and anemia (3.3%). The most common adverse reactions resulting in dose reduction of belzutifan were fatigue (8.2%), anemia (3.3%) and hypoxia (1.6%). Belzutifan was discontinued due to adverse reaction in 4 patients.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies with belzutifan are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Table 2: Adverse reactions for WELIREG 120 mg Once Daily*

System Organ Class	Adverse Drug Reaction
Blood and lymphatic disorders	
Very Common	anemia
Nervous system disorders	
Very Common	dizziness
Respiratory, thoracic and mediastinal disorders	
Very Common	dyspnea
Common	hypoxia
Gastrointestinal disorders	
Very Common	nausea
General disorders and administration site disorders	
Very Common	fatigue
Investigations	
Very Common	weight increased

*Adverse reaction frequencies presented in Table 2 may contain contributions from the underlying disease.

Serious adverse events of haemorrhage intracranial were reported in 2 subjects (3.3%) and 1 subject discontinued treatment due to adverse event of haemorrhage intracranial.

7.2 Advanced Renal Cell Carcinoma

The safety of belzutifan was evaluated in a Phase 3 clinical study (LITESPARK-005), in 372 patients with advanced RCC. Patients were treated with 120 mg belzutifan once daily. The median duration of exposure to belzutifan was 7.6 months (range 0.1 to 35.8 months).

The most common adverse reactions under treatment with belzutifan were anemia (83%), fatigue (31%), dyspnea (15%), hypoxia (15%), nausea (18%) and dizziness (12%).

The most common adverse reactions resulting in dose interruption of belzutifan were anemia (8.6%), hypoxia (5.6%), fatigue (1.6%), dizziness (1.6%), dyspnea (1.6%) and nausea (1.3%). The most common adverse reactions resulting in dose reduction of belzutifan were hypoxia (5.6%) and anemia (3.0%). Belzutifan was discontinued due to adverse reaction in 5.9% of patients.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies of belzutifan are listed in Table 3. These reactions are presented by system organ class and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Table 3: Adverse reactions in patients treated with belzutifan 120 mg once daily in adult patients with advanced RCC

System Organ Class	Adverse reactions
Blood and lymphatic disorders	
Very common	Anemia*
Nervous system disorders	
Very common	Dizziness
Respiratory, thoracic and mediastinal disorders	
Very Common	Dyspnea, hypoxia
Gastrointestinal disorders	
Very Common	Nausea
General disorders and administration site disorders	
Very Common	Fatigue
Investigations	
Common	Weight increased

*Anemia includes anemia and haemoglobin decreased

The safety of belzutifan was also evaluated in a Phase 1 clinical study (Study-001), in 58 patients with non-VHL disease-associated advanced solid tumors, treated with belzutifan 120 mg once daily. Study-001 patients differed from VHL-associated RCC patients (LITESPARK-004). Study-001 patients were older, had worse ECOG PS, had metastatic disease, had prior therapies, had more comorbidities, and had lower baseline hemoglobin levels at treatment initiation. Study-001 had a median duration of exposure to belzutifan of 25.4 weeks (range: 1.1 to 145.9 weeks). The adverse reactions under treatment with belzutifan in Study-001 were anemia (76%), fatigue (71%), dyspnea (47%), nausea (35%), hypoxia (29%), dizziness (22%) and weight increased (10%). The adverse reactions resulting in dose interruption of belzutifan were hypoxia (10.3%), anemia (8.6%), dyspnea (5.2%), fatigue (1.7%) and nausea (1.7%). The adverse reactions resulting in dose reduction of belzutifan were hypoxia (3.4%), nausea (1.7%) and fatigue (1.7%). The adverse reactions resulting in discontinuation were hypoxia (3.4%) and fatigue (1.7%).

8. OVERDOSAGE

There is no specific treatment for WELIREG overdose. In cases of suspected overdose, if necessary, consider withholding WELIREG and instituting supportive care. The highest dose of WELIREG studied clinically was 240 mg total daily dose (120 mg twice a day or 240 mg once a day). Grade 3 hypoxia occurred at 120 mg twice a day and Grade 4 thrombocytopenia occurred at 240 mg once daily.

9. CLINICAL STUDIES

9.1 Clinical studies in adult patients with von Hippel-Lindau (VHL) disease associated tumors

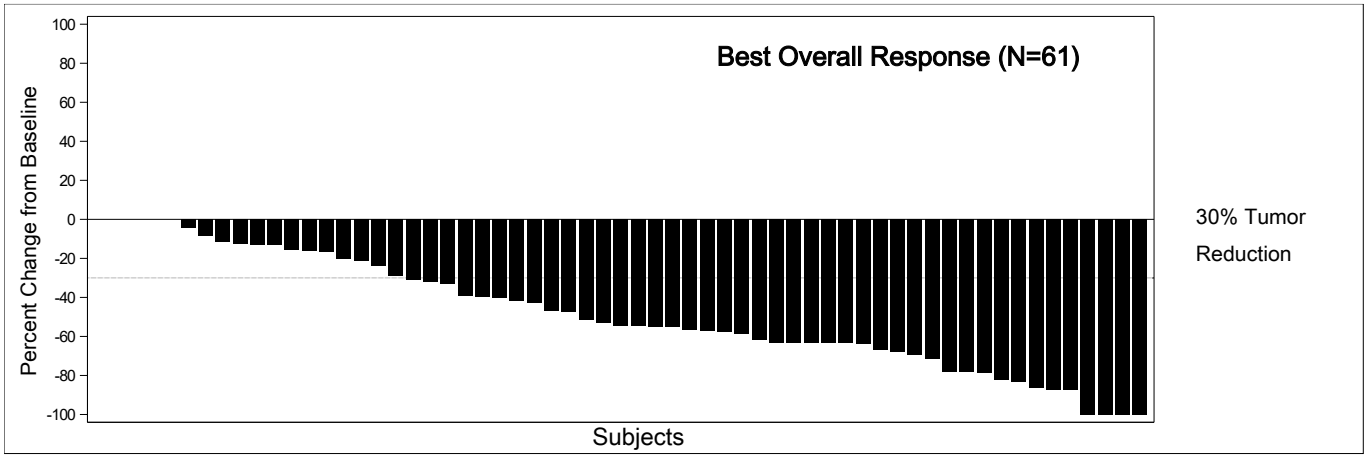
The efficacy of WELIREG was investigated in LITESPARK-004, an open-label Phase 2 clinical trial in 61 patients with VHL disease who had at least one measurable solid tumor (as defined by RECIST v1.1) localized to the kidney and who did not require immediate surgery. Patients received WELIREG at a dose of 120 mg once daily. Patients were evaluated radiologically approximately 12 weeks after initiation of treatment and every 12 weeks thereafter. Treatment was continued until progression of disease or unacceptable toxicity. The study excluded patients who had any evidence of metastatic disease, either RCC or other VHL disease-associated tumors, an immediate need for surgical intervention for tumor treatment, any major surgical procedure completed within 4 weeks prior to study enrollment, any major cardiovascular event within 6 months prior to study drug administration, or prior systemic treatments for VHL disease-associated RCC.

The study population characteristics were: median age of 41 years, 3.3% age 65 or over; 52.5% male; 90.2% White; and 82.0% had an ECOG PS of 0 and 16.4% had an ECOG PS of 1. Seventy-seven percent of patients had prior RCC surgical procedures. Other VHL disease-associated tumors in patients included pancreatic lesions (100.0%) of which 36.1% were pancreatic neuroendocrine tumors, CNS hemangioblastomas (82.0%), and retinal angiomas (19.7%).

The primary efficacy endpoint for the treatment of VHL disease-associated RCC was objective response rate (ORR) measured by Integrated Radiology and Oncology Assessment (IRO) assessment using RECIST v1.1 as assessed by a central independent review committee (IRC). Additional efficacy endpoints included disease control rate (DCR), response duration, progression-free survival (PFS), time to response (TTR), and time to surgery (TTS). Radiographic endpoints were

assessed by IRC using RECIST v1.1. The clinical benefit of WELIREG in reducing RCC tumor size, and slowing the growth of tumors, was supported by pre-treatment and post-treatment linear growth rate of 3.26 and -3.42 mm/year, respectively in LITESPARK-004. A total of 91.8% of participants (56/61) had a decrease in the sum of target tumor diameters (Figure 1). After a median follow-up time of 37.7 months, seven out of 61 (11.5%) patients required an RCC tumor reduction procedure during treatment. In a natural history study of VHL, RCC patients undergoing active surveillance and local therapy, 30% and 57% of patients, respectively, had ≥ 1 renal surgery within 2 and 5 years of follow-up. Table 4 summarizes the efficacy results for VHL disease-associated RCC tumors in LITESPARK-004.

Figure 1: Waterfall Plot- Percentage Change in Total Sum of RCC Target Lesions Diameters From Baseline to Post-Baseline Maximum % Reduction (RECIST 1.1)- IRC Efficacy Analysis Set – Patients with Evaluable RCC Tumors at Baseline



Subjects without either post-baseline evaluable lesion measurements or target lesions or with all post-baselinenon-evaluable time-point responses appear as blank on the right of the figure. Number (%) of patients with maximum % reduction in sum of diameters of target lesions < 0 = 56 (91.8) Date of Data Cut-off: 01APR2022

Table 4: Efficacy Results for WELIREG for VHL Disease-Associated RCC Tumors

Endpoint	WELIREG 120 mg daily n=61
Objective Response Rate	
ORR* % (95% CI)	63.9% (50.6, 75.8)
Complete response	6.6%
Partial response	57.4%
Stable disease	34.4%
Disease Control Rate†	98.4%
Response Duration‡	
Median in months (range)	NE (5.4+, 35.8+)
% (n) with duration ≥ 12 months	100.0% (35)
Time to Response	
Median in months (range)	11.1 (2.7, 30.5)
Time to Surgery	
Median in months (95% CI)	NE (NE, NE)
PFS‡	
Median in months (95% CI)	NE§ (38.5, NE)
24-month PFS rate	94.6%

* Response: Best objective response as confirmed complete response or partial response

† Based on best response of stable disease or better

‡ Based on Kaplan-Meier estimates

§ Reliable median could not be estimated due to the number of progression events and too few patients were at risk at the maximum follow up months

\+ Denotes ongoing response

NE = Not estimable

Data cut-off: April 1, 2022

Efficacy endpoints for the treatment of other VHL disease-associated tumors included ORR, DCR and response duration, as assessed by IRC using RECIST v1.1. These results are shown in Table 5.

Table 5: Efficacy Results for WELIREG for Other VHL Disease-Associated Tumors

	WELIREG 120 mg daily n=61	
Endpoint	**Patients with Evaluable Pancreatic Neuroendocrine Tumors n=22**	**Patients with Evaluable CNS Hemangioblastomas n=50**
Objective Response Rate		
ORR % (95% CI)	90.9% (70.8, 98.9)	44% (30.0, 58.7)
Complete response	31.8%	8.0%
Partial response	59.1%	36.0%
Stable disease	9.1%	46.0%
Disease Control Rate†	100.0%	90.0%
Response Duration‡		
Median in months (range)	Not reached (11.0+, 37.3+)	Not reached (3.7+, 38.7+)
% (n) with duration ≥ 12 months	100.0% (12)	90.2% (16)

† Based on best response of stable disease or better

‡ Based on Kaplan-Meier estimates

\+ Denotes ongoing response

Data cut-off: April 1, 2022

9.2 Clinical studies in adult patients with advanced renal cell carcinoma (RCC)

The efficacy of belzutifan was evaluated in LITESPARK-005, an open-label, randomized, active-controlled Phase 3 clinical study comparing belzutifan with everolimus in 746 patients with unresectable, locally advanced or metastatic clear cell RCC that has progressed following PD-1/L1 checkpoint inhibitor and VEGF receptor targeted therapies either in sequence or in combination. Patients could have received up to 3 prior treatment regimens and must have measurable disease per RECIST v1.1. Patients were randomized in a 1:1 ratio to receive 120 mg belzutifan or 10 mg everolimus by oral administration once daily. Randomization was stratified by International Metastatic RCC Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and number of prior VEGF receptor targeted therapies (1 versus 2-3).

Patients were evaluated radiologically at Week 9 from the date of randomization, then every 8 weeks through Week 49, and every 12 weeks thereafter.

Among the 746 patients in LITESPARK-005, the baseline characteristics were: median age 63 years (range 22-90 years), 42% age 65 or older; 78% male; 79% White; 12% Asian; 1.1% Black or African American; 43% ECOG performance status 0 and 55% ECOG performance status 1. Prior therapies: 13% of patients had 1 prior line of therapy, 43% had 2 prior lines of therapy and 43% had 3 prior lines of therapy; 49% received 2 to 3 prior VEGF receptor targeted therapies. Patient distribution by IMDC risk categories was 22% favorable, 66% intermediate, and 12% poor.

The primary efficacy outcome measures were Progression-Free Survival (PFS) measured by BICR using RECIST v1.1, and Overall Survival (OS). Secondary efficacy outcome measures included objective response rate (ORR), and duration of response (DOR) by BICR using RECIST v1.1.

The trial demonstrated a statistically significant improvement of PFS for patients randomized to WELIREG compared with everolimus. The efficacy results for advanced RCC in LITESPARK-005 are summarized in Table 6.

Table 6: Efficacy Results (BICR assessment) for Belzutifan in LITESPARK-005

Efficacy Outcome Measure	Belzutifan n=374	Everolimus n=372
PFS, % (n)*		
Number of events	69% (257)	70% (262)
Progressive disease	63% (234)	60% (222)
Median PFS in months (95% CI)†	5.6 (3.9, 7.0)	5.6 (4.8, 5.8)
Hazard ratio‡ (95% CI)	0.75 (0.63, 0.90)	
p-Value	0.00077	
OS, % (n)§		
Number of events	68% (254)	70% (259)
Median OS in months (95% CI)	21 (18, 24)	18 (16, 22)
Hazard ratio (95% CI)	0.92 (0.77, 1.10)	
p-Value¶	0.1764	
ORR, % (n) (95% CI)*	22% (82) (17.8, 26.5)	3.5% (13) (1.9, 5.9)
Complete response	2.7% (10)	0% (0)
Partial response	19% (72)	3.5% (13)
p-Value	<0.00001	
Duration of Response*		
Median in months (range)	NR (1.7+ - 23.2+)	17.2 (3.8 – 18.0+)
% with DoR ≥ 12 months†	74%	68%

* Based on first pre-specified interim analysis for PFS with median follow up time of 14 months.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on the stratified Cox regression model.

§ Based on the pre-specified final analysis for OS with median follow up time of 20 months.

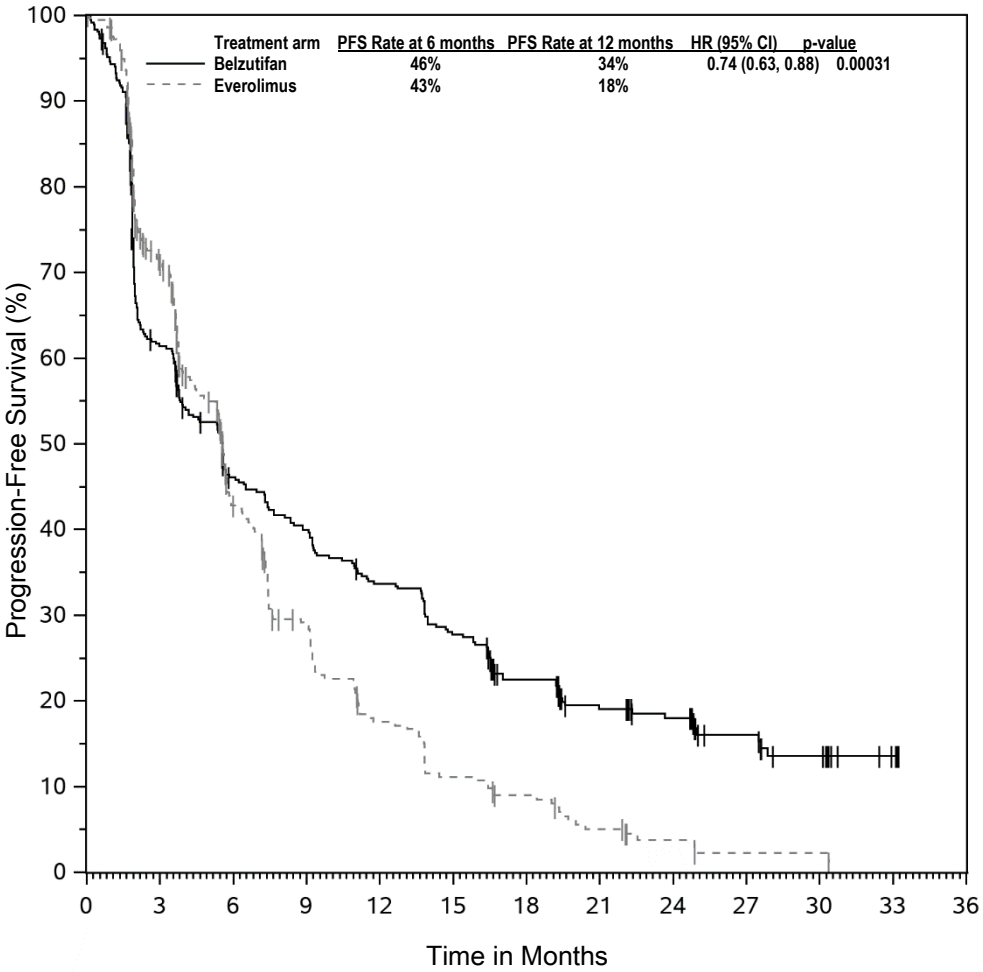
¶ Not statistically significant after adjustment for multiplicity.

+ Indicates there is no progressive disease by the time of last disease assessment.

At a subsequent pre-specified analysis with median follow-up time of 17.8 months (range: 0.2 - 39.1 months) there were 289 PFS events for WELIREG and 276 PFS events for everolimus. The median PFS was 5.6 months (95% CI: 3.8, 6.5) for WELIREG versus 5.6 months (95% CI: 4.8, 5.8) for everolimus. The PFS hazard ratio was 0.74 (95% CI: 0.63, 0.88) (Figure 2). The median duration of response was 19.5 (range: 1.9 - 31.6+) for WELIREG versus 13.7 (range: 3.8 – 21.2+) for everolimus. Based on Kaplan-Meier estimates, patients with a DOR ≥ 12 months was 73% for WELIREG versus 62% for everolimus.

The median Time to Response (TTR) was 3.8 months (range: 1.7 - 22.0) in the belzutifan group and 3.7 months (range: 1.8 - 5.4) in the everolimus group. ORR analysis demonstrated ORR of 22.7% for WELIREG versus 3.5% for everolimus.

Figure 2: Kaplan-Meier Curve for Radiographic Progression-free Survival in LITESPARK-005



10. CLINICAL PHARMACOLOGY

10.1 Therapeutic Class

Hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor.

Pharmacotherapeutic group: other antineoplastic agents, ATC code: L01XX74.

10.2 Mechanism of Action

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilization and accumulation of HIF-2α . Upon stabilization, HIF-2α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1β) to form a transcriptional complex that regulates expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth (including CCND1, VEGFA, SLC2A1 (GLUT1), IGFBP3, TGFa, AXL, CXCR4, IL6). Belzutifan binds to HIF-2α , and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α -HIF-1β interaction, leading to reduced transcription and expression of HIF-2α target genes. *In vivo*, belzutifan demonstrated anti-tumor activity in mouse xenograft models of renal cell carcinoma.

10.3 Pharmacodynamics

Circulating plasma levels of erythropoietin (EPO) were monitored in patients as a pharmacodynamic marker of HIF-2α inhibition. Reductions in EPO were observed to be dose/exposure dependent and showed a plateauing effect on reduction at exposures achieved with doses above 120 mg once daily. The maximum EPO suppression occurred following 2 weeks of consecutive dosing of WELIREG (mean percent decrease from baseline of approximately 60%). Mean EPO levels gradually returned to baseline values after 12 weeks of treatment.

The incidence of Grade 3 anemia increased with higher belzutifan exposure in patients with baseline hemoglobin levels <12 g/dL *[see 4 WARNINGS AND PRECAUTIONS]*.

Cardiac Electrophysiology

At the recommended dose (120 mg once daily) for WELIREG, there were no clinically relevant effects on the QTc interval.

Pharmacogenomics

Belzutifan is primarily metabolized by UGT2B17 and CYP2C19. The activity of these enzymes varies among individuals who carry different genetic variants, which may impact belzutifan concentrations. Poor metabolizers are individuals who are considered to have no enzyme activity. Approximately 15% of Caucasians, 11% of Latinos, 6% of African Americans, 38% of South Asians, and 70% of East

Asians are UGT2B17 poor metabolizers. Approximately 2% of Caucasians, 1% of Latinos, 5% of African Americans, 8% of South Asians, and 13% of East Asians are CYP2C19 poor metabolizers. Approximately 0.3% of Caucasians, 0.1% of Latinos, 0.3% of African Americans, 3% of South Asians, and 9% of East Asians are dual UGT2B17 and CYP2C19 poor metabolizers. Expected frequencies in the Japanese population for the UGT2B17, CYP2C19, and dual UGT2B17 and CYP2C19 poor metabolizers are approximately 77%, 19%, and 15%, respectively. Expected frequencies in the United States population for the UGT2B17, CYP2C19, and dual UGT2B17 and CYP2C19 poor metabolizers are approximately 16%, 3%, and 0.5%, respectively based on the reported proportion of the US population represented by major racial/ethnic groups.

The impact of CYP2C19 and UGT2B17 poor metabolizers on belzutifan exposure was assessed in a population PK analysis. Based on the population PK model, patients who are CYP2C19, UGT2B17, or dual UGT2B17 and CYP2C19 poor metabolizers, are projected to have 1.3-, 2.7- or 3.3-fold the exposures (steady-state $AUC_{0\text{-}24hr}$), respectively, compared to a typical reference patient (UGT2B17 extensive metabolizer, CYP2C19 extensive/intermediate metabolizer) for the recommended dose. No dose adjustment is recommended based on exposure-response analyses for efficacy and safety and the risk-benefit profile.

10.4 Pharmacokinetics

General Introduction

The pharmacokinetics of belzutifan are similar in healthy subjects and patients with solid tumors including advanced RCC. C_{max} and AUC increase proportionally over a dose range of 20 mg to 120 mg. Based on population PK analysis, the simulated geometric mean steady-state (CV%) C_{max} is 1.5 µg/mL (46%) and $AUC_{0\text{-}24hr}$ is 20.8 µg• hr/mL (64%) in patients treated with 120 mg belzutifan. Steady-state is reached after approximately 3 days.

Absorption

Following single-dose oral administration of 120 mg of WELIREG, peak plasma concentrations (median T_{max}) of belzutifan occurred at 1 to 2 hours post dose.

Effect of Food

A high-fat, high-calorie meal delayed peak belzutifan concentration by approximately 2 hours but, had no effect on exposure (AUC). There was a modest decrease of C_{max} by 24% following consumption of a high-fat, high-calorie meal, but this was not clinically meaningful. Therefore, WELIREG can be taken without regard to food.

Distribution

Based on the population PK analysis, the mean (CV%) volume of distribution is 120 L (28.5%). Plasma protein binding of WELIREG is 45%. The blood-to-plasma concentration ratio of WELIREG is 0.88.

Metabolism

Belzutifan is primarily metabolized by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4. Both UGT2B17 and CYP2C19 display genetic polymorphisms *[see 10. CLINICAL PHARMACOLOGY, 10.3 Pharmacodynamics]*.

Elimination

Based on the population PK analysis, the mean (CV%) clearance is 5.89 L/hr (60.6%) and the mean elimination half-life is approximately 14 hrs.

Excretion

Following oral administration of radiolabeled belzutifan to healthy subjects, approximately 49.6% of the dose was excreted in urine and 51.7% in feces (primarily as inactive metabolites). Approximately 6% of the dose was recovered as parent drug in urine.

Special Populations

Renal Impairment

No relevant increase in exposure (AUC) was observed for subjects with mild or moderate renal impairment. Renal impairment (as evaluated by eGFR) was not identified as a significant covariate in the population pharmacokinetic analysis. The pharmacokinetics of belzutifan have not been studied in patients with severe renal impairment *[see 2. DOSAGE AND ADMINISTRATION, 2.5 Renal Impairment and 6. USE IN SPECIFIC POPULATIONS, 6.6 Renal Impairment]*.

Hepatic Impairment

No relevant increase in exposure (AUC) was observed for subjects with mild hepatic impairment (using NCI index) based on population pharmacokinetic analysis. The pharmacokinetics of belzutifan have not been studied in patients with moderate or severe hepatic impairment *[see 2. DOSAGE AND ADMINISTRATION, 2.6 Hepatic Impairment and 6. USE IN SPECIFIC POPULATIONS, 6.7 Hepatic Impairment].*

Dual UGT2BI7 and CYP2C19 Poor Metabolizers

Patients who are poor metabolizers of UGT2B17 and CYP2C19 had higher belzutifan AUC *[see 10 CLINICAL PHARMACOLOGY]*.

Pediatric

No studies with belzutifan have been performed in pediatric patients.

Effects of Age, Gender, Ethnicity, Race, and Body Weight

Based on a population pharmacokinetic analysis, age, gender, ethnicity, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of belzutifan. Potential differences in exposure across races are possible due to different frequencies of metabolizing enzymes *[see 10. CLINICAL PHARMACOLOGY, 10.3 Pharmacodynamics]*.

10.5 Drug Interaction Studies

In Vitro Assessment of Drug Interactions

Belzutifan is a substrate of UGT2B17, CYP2C19 and CYP3A4. Active transport is not an important determinant of belzutifan disposition. Belzutifan is not an inhibitor of CYP enzymes, UGT enzymes, or transporters with the exception of MATE2K. Belzutifan does not induce CYP1A2 or CYP2B6, however, WELIREG induces CYP3A4 in a concentration dependent manner.

In Vivo Assessment of Drug Interactions

In a clinical study, repeat administration of WELIREG 120 mg QD resulted in a 40% reduction in midazolam AUC, an effect consistent with a weak CYP3A4 inducer. Based on PBPK modeling, WELIREG may exhibit moderate CYP3A4 induction in patients who have higher belzutifan plasma exposures *[see 10. CLINICAL PHARMACOLOGY, 10.3 Pharmacodynamics].*

11. NAME OF THE DRUG

WELIREG 40 mg (belzutifan 40 mg)

12. PHARMACEUTICAL FORM

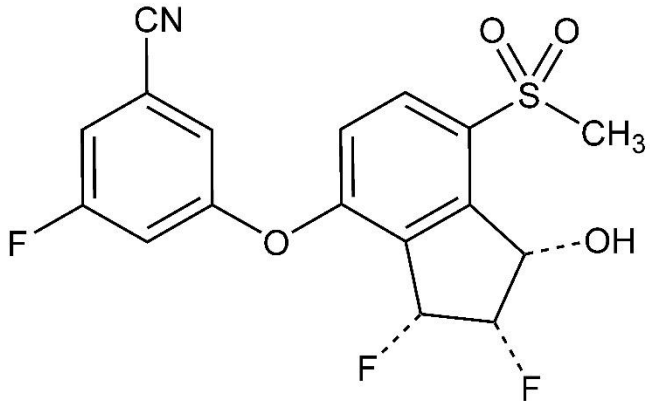
WELIREG 40 mg tablet is a blue, oval, film-coated tablet with a length of 13.36 mm and a width of 8.20 mm, with “177” on one side.

13. PHARMACEUTICAL PARTICULARS

13.1 Chemistry

The chemical name of belzutifan is 3-[[(1S,2S,3R)-2,3-Difluoro-2,3-dihydro-1-hydroxy-7-(methylsulfonyl)-1H-inden-4-yl]oxy]-5-fluorobenzonitrile. The molecular formula is $C_{17}H_{12}F_3NO_4S$ and the molecular weight is 383.34 Daltons.

The chemical structure is:



Belzutifan is a white to light brown powder that is soluble in acetonitrile, dimethoxyethane and acetone, sparingly soluble in ethyl acetate, very slightly soluble in isopropanol and toluene, and insoluble in water.

13.2 Composition

Active Ingredient

Each WELIREG tablet contains 40 mg of belzutifan.

Inactive Ingredients (List of excipients)

WELIREG tablets contain the inactive ingredients: croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide.

The film-coat contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol-part hydrolyzed, talc, titanium dioxide.

Excipients of Special Interest

Not applicable.

13.3 Storage

Store below 30°C.

13.4 Shelf Life

Refer to outer carton.

13.5 Availability (a.k.a. Nature and contents of container)

WELIREG is available in aluminium / aluminium blisters. Each pack contains 30 film-coated tablets. Each multipack contains 90 (three packs of 30) film-coated tablets, not to be sold separately.

Product Owner:

Merck Sharp & Dohme LLC
126 East Lincoln Ave.
P.O. Box 2000
Rahway, New Jersey 07065
USA

Date of revision: April 2025

MSD