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

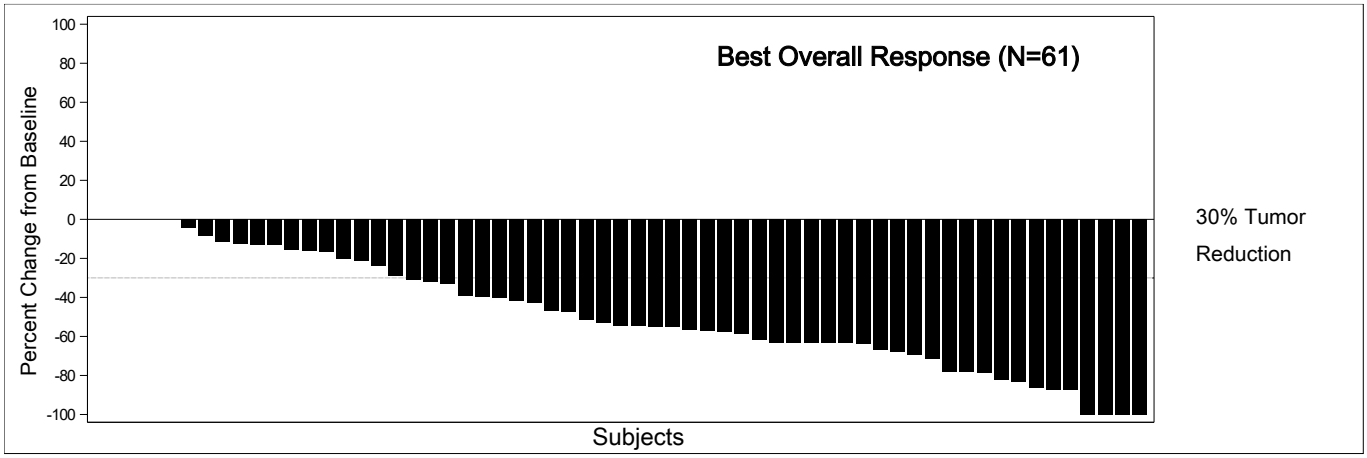
The efficacy of WELIREG was investigated in LITESPARK-004, an open-label Phase 2 clinical trial in 61 patients with VHL disease who had at least one measurable solid tumor (as defined by RECIST v1.1) localized to the kidney and who did not require immediate surgery. Patients received WELIREG at a dose 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.

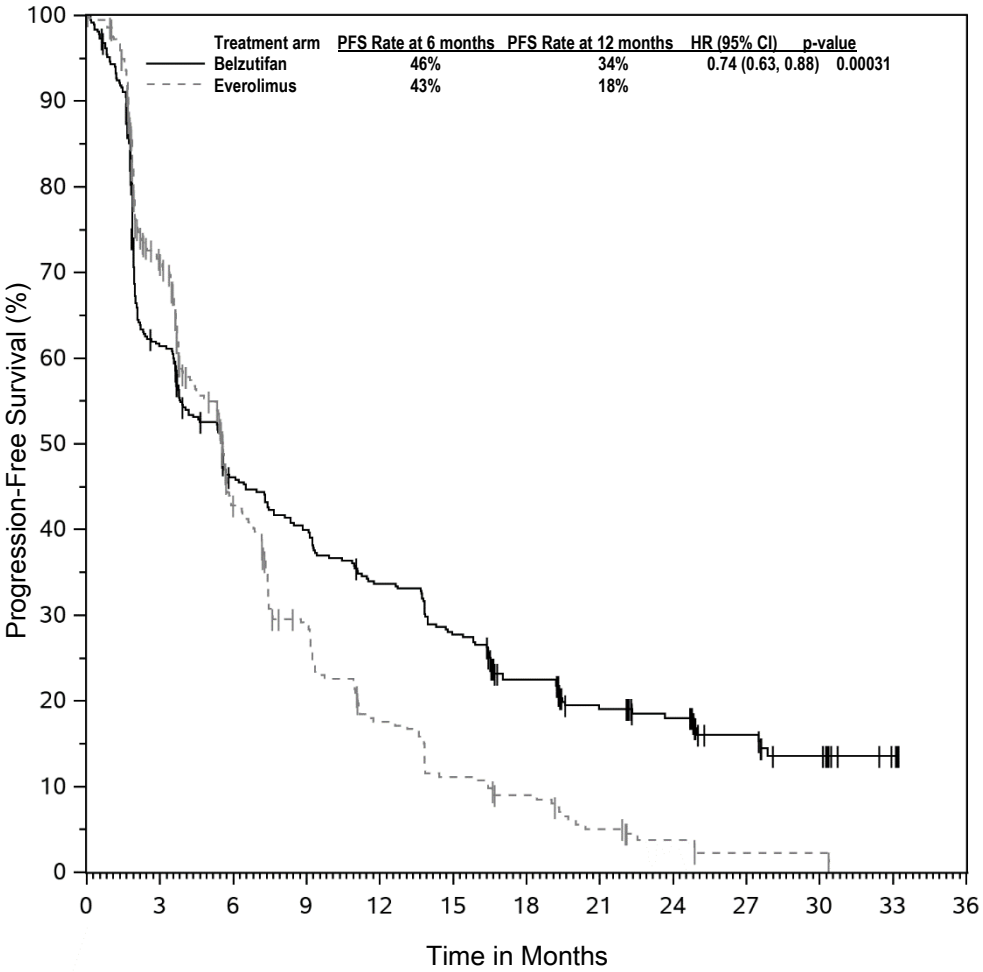
¶ Not statistically significant after adjustment for multiplicity.

+ 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

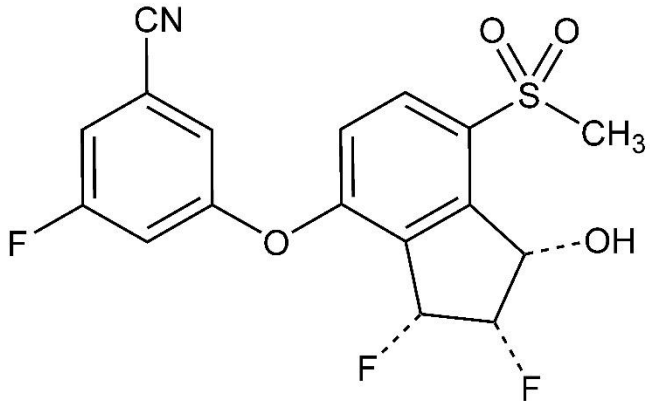
WELIREG 40 mg tablet is a blue, oval, film-coated tablet with a length of 13.36 mm and a width of 8.20 mm, with “177” on one side.

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:

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USA

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MSD