MAT-XU-2205247 (V4.0) | January 2024.
Prescribing information can be found on the last 2 pages.

REZUROCK® ▼
(belumosudil) tablets

THE ROCKSTAR STUDY (KD025-213)

Summary

REZUROCK is indicated for the treatment of patients aged 12 years and older with chronic graft-versus-host disease (chronic GVHD) who have received at least two prior lines of systemic therapy

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to the Sanofi drug safety department on Tel: 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com

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REZUROCK was evaluated in the pivotal ROCKstar (KD025-213) study for patients with cGVHD[1]

Patients received REZUROCK after failure of 2 to 5 previous lines of systemic therapy[1]

SELECT ROCKstar STUDY PATIENT BASELINE CHARACTERISTICS[1,2,3]

Characteristics	REZUROCK 200 mg once daily (n=66)[a]
Median age, y (range)	53 (21-77)
Male, n (%)	42 (64)
Median prior lines of systemic therapy, n	3 (2-6)
Median time from cGVHD diagnosis to enrollment, mo (range)	25 (2-162)
Median prednisone-equivalent dose at enrollment, mg/kg/d (range)	0.20 (0.03-0.95)
Concomitant PPI use, n (%)	33 (50)
≥4 organs involved, n (%)	33 (50)
Previous aGVHD, n (%)	42 (64)
Refractory to prior line of systemic therapy, n (%)	44 (79)
NIH-defined cGVHD severity, n (%)	
Severe	46 (70)
Moderate	18 (27)
Mild	2 (3)

Study design[1]: ROCKstar was a pivotal phase 2, open-label, non-controlled, randomized, multicenter study that evaluated the efficacy and safety of REZUROCK in patients with cGVHD after receiving 2 to 5 prior lines of systemic therapy.

Treatment consisted of REZUROCK 200 mg and was administered continuously until clinically significant progression of cGVHD or unacceptable toxicity.

- **Primary end point:** Best ORR at any time, defined as the proportion of subjects who achieved CR or PR according to the 2014 NIH cGVHD Consensus Criteria[1]
- **Prespecified key secondary end points (not powered to show statistical significance):** safety, DOR, TTR, LSS score, change in CS/CNI dose, FFS and OS[1]

The most common prior systemic therapy[b] was corticosteroids (98%), followed by calcineurin inhibitors (tacrolimus 62% and sirolimus 47%), ECP (48%), ibrutinib (34%) and ruxolitinib (29%)[3]

aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CNI, calcineurin inhibitor; CR, complete response; DOR, duration of response; FFS, failure-free survival; LSS, Lee Symptom Scale; MHRA, Medicines and Healthcare Products Regulatory Agency; NIH, National Institutes of Health; ORR, overall response rate; PPI, proton pump inhibitor; PR, partial response; TTR, time to response.

[a]The final MHRA interpretation of the ROCKstar study omitted 1 patient from the REZUROCK 200-mg once-daily arm. As a result, there are minor differences between the ROCKstar publication, where n=66, and the Summary of Product Characteristics, where n=65.

[b]Some of these medicines do not have a licence in Great Britain for the treatment of cGvHD.

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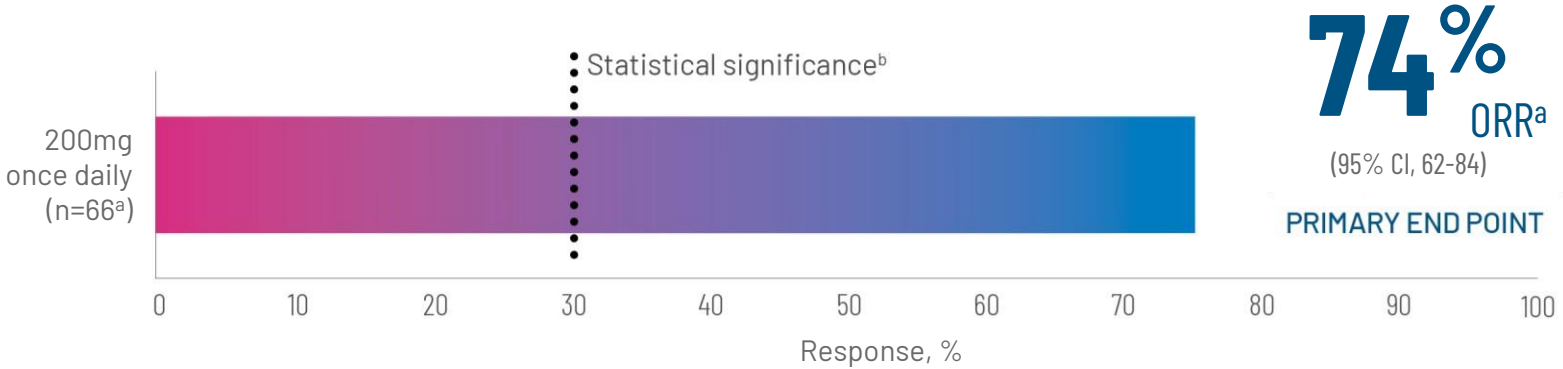
Clinically meaningful overall response rates[1]

STATISTICALLY SIGNIFICANT ORR[c] FOLLOWING TREATMENT WITH REZUROCK 200mg ONCE DAILY[1]



Primary end point: Best ORR at any time, defined as the proportion of subjects who achieved CR or PR according to the 2014 NIH cGVHD Consensus Criteria[1]

CR, n=4 (6%). PR, n=45 (68%)[1]

CR, complete response; mITT, modified intent-to-treat; ORR, overall response rate; PR, partial response.

[a]Based on mITT population (n=66).[1]

[b]Statistical significance was achieved if the lower bound of the 95% CI of ORR exceeded 30%.[1] Clopper Pearson interval (exact) method used for calculation of 95% CIs, and p values are adjusted through Hochberg method of multiplicity correction corresponding to the null hypothesis of ORR ≤30%.[1]

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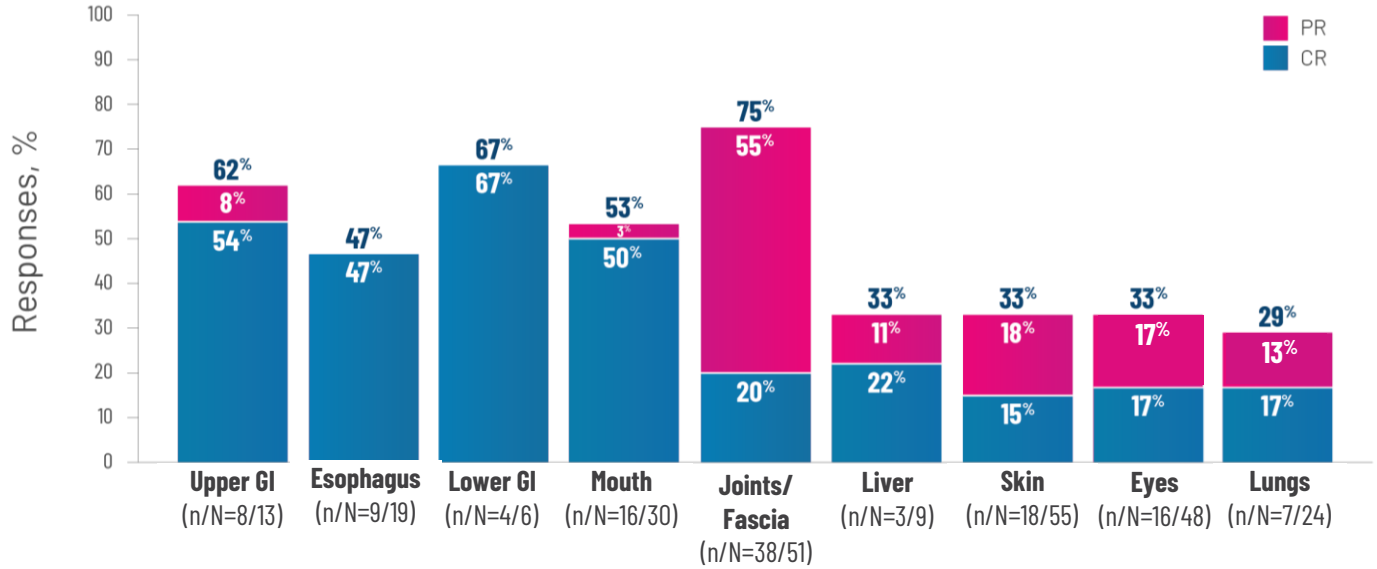
Response across all evaluated organs[1,4]

Secondary end point: Response rate by organ system.[1]

RESPONSES BY ORGAN SYSTEM WITH REZUROCK 200 mg ONCE DAILY IN THE mITT POPULATION (n=66)[4]



CR, complete response; GI, gastrointestinal; mITT, modified intent-to-treat; PR, partial response.

[a]Primary end point was best ORR at any time, defined as the proportion of subjects who achieved CR or PR according to the 2014 NIH cGVHD Consensus Criteria[1]. CR defined as the resolution of all manifestations in each organ or site. PR defined as improvement in ≥1 organs or sites without progression in any other organ or site[5]. Percentages may not add up to the total due to rounding.

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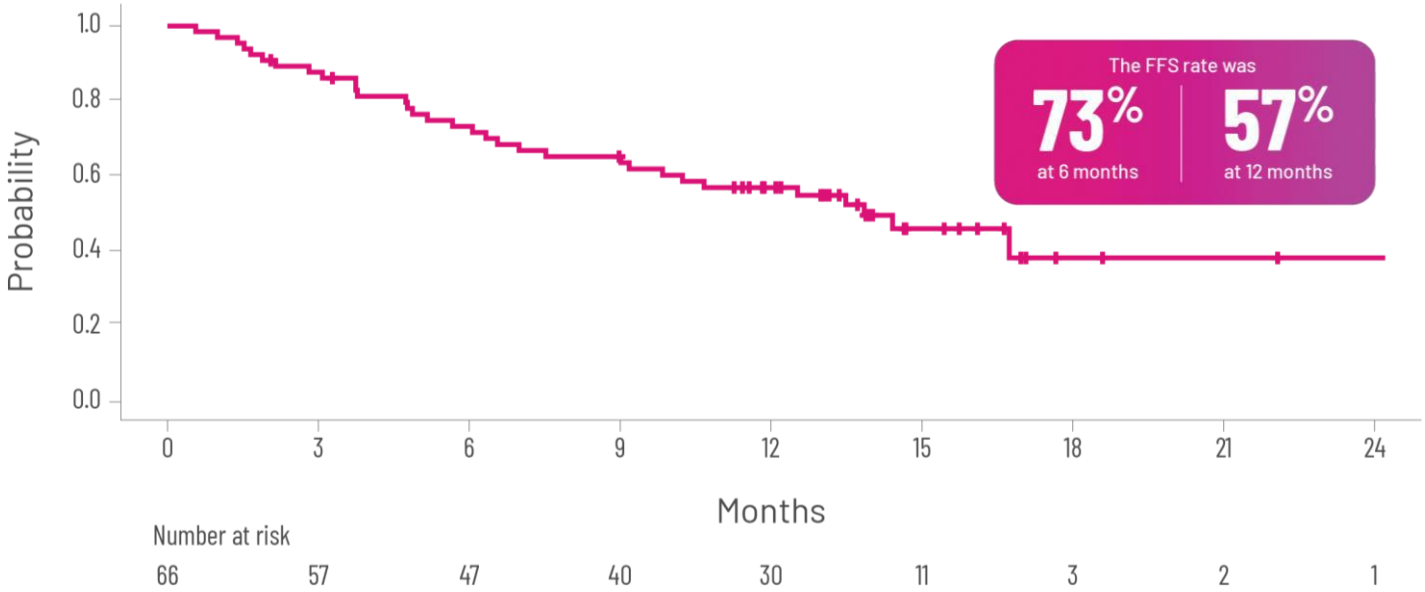
FFS rates with REZUROCK

Secondary end point: FFS, defined as the absence of relapse, nonrelapse mortality or a need for additional systemic therapy.[1]

FFS[a] WITH REZUROCK 200 mg ONCE DAILY IN THE mITT POPULATION[2]



Adapted from Data on File, Sanofi[4]

FFS, failure-free survival; mITT, modified intent-to-treat.

[a]Kaplan-Meier curve of estimated FFS.

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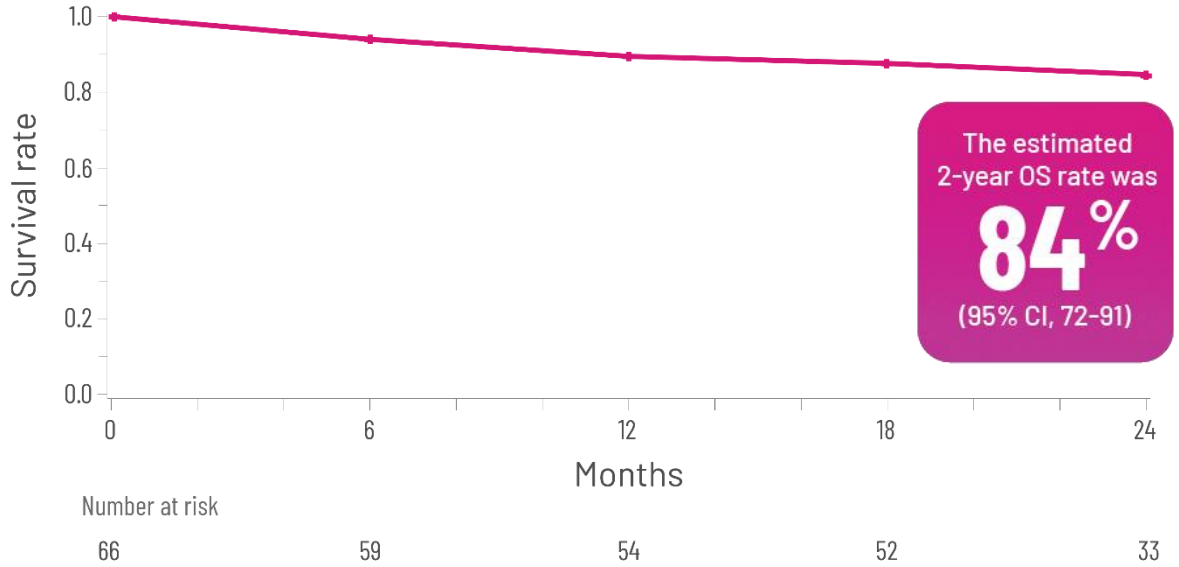
Estimated OS rates with REZUROCK

Secondary end point: OS, defined as the time from the first dose of REZUROCK to the date of death due to any cause.[1,2]

OS[a] WITH REZUROCK 200 mg ONCE DAILY IN THE mITT POPULATION[2]



Adapted from Cutler C et al., 2021[1]

mITT, modified intent-to-treat; OS, overall survival.

[a]Kaplan-Meier curve of estimated OS.

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Most responses were seen between 4 and 8 weeks[2]

CUMULATIVE RESPONSE RATES OVER TIME IN THE RESPONDER POPULATION WITH REZUROCK 200 mg ONCE DAILY (n/N=48/66)[2]

4.4 WEEKS	Median time to response was 4.4 weeks (3.7-40.6)[3]
100.3 WEEKS	Median time from first response to the initiation of new systemic cGVHD therapy was 100.3 weeks (54.14-NA)[2]
63%	OF RESPONSES were observed between weeks 4 and 8[2]
96%	OF RESPONSES were observed by week 24[2]

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Responses were seen across all patient types[1,2]

ORRs OBSERVED ACROSS KEY SUBGROUPS IN THE 200-mg ONCE-DAILY ARM[1,2]

The subgroups have limited numbers and were not powered for planned efficacy comparisons or inference. These are therefore exploratory.

86%
in patients with an **EARLY cGVHD DIAGNOSIS[2]**, defined as <28 months from initial diagnosis (n/N=30/35)

74%
in patients with **SEVERE cGVHD[2]** (n/N=34/46)

70%
in patients with **cGVHD INVOLVING ≥4 ORGANS[2]** (n/N=23/33)

67%
in patients who received **>3 PRIOR LINES OF SYSTEMIC THERAPY[2]** (n/N=20/30)

cGVHD, chronic graft-versus-host disease; ORR, overall response rate.

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Change in QOL scores

59%

OF PATIENTS[a] REPORTED IMPROVEMENT IN QOL[1]

IMPROVEMENTS IN PATIENT-REPORTED QOL[1]

(≥7-point reduction in LSS summary score) with REZUROCK 200 mg once daily in the mITT population in an exploratory analysis[1]

- Both responders (69%) and nonresponders (29%) had improved QOL scores[1]

The Lee Symptom Scale (LSS) is a 30-item, 7-subscale symptom scale and QOL measurement tool that evaluates the AEs of cGVHD in the categories of skin, vitality, lung, nutritional status, psychological functioning, eye and mouth.[6]

These were not tested for statistical significance.

LSS, Lee Symptom Scale; mITT, modified intent-to-treat; QOL, quality of life.

[a]Based on mITT population (n=66).[1]

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Change in dependence on CS and CNI therapies

CHANGE IN USE OF CS AND CNI THERAPIES[1,2]

This data is descriptive.

Dose reductions and discontinuations in patients who received CS therapy[1]

64% (n/N=42/66) of patients in the 200-mg once-daily arm reduced their **CS DOSES**.

The mean percentage change in CS dose reduction was **43%** in the mITT population who received REZUROCK 200 mg once daily (**49%** in responders and **22%** in nonresponders).[a]

20% (n/N=13/66) of patients in the 200-mg once-daily arm **DISCONTINUED CS THERAPY**.

Dose reductions and discontinuations in patients who received CNI therapy[2]

29% (n/N=7/24) of patients in the 200-mg once-daily arm reduced their **CNI DOSES**.

8% (n/N=2/24) of patients in the 200-mg once-daily arm **DISCONTINUED CNI THERAPY**.

CNI, calcineurin inhibitor; CR, complete response; CS, corticosteroid; PR, partial response.

[a]Nonresponders were defined as patients with CR or PR in ≥1 organ, accompanied by progression in another organ (considered progression); outcomes that did not meet the criteria for CR, PR, progression or mixed response; or progression in ≥1 organ or site without a response in any other organ or site.[2]

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The ROCKstar Study: Safety and Tolerability[1]

Commonly reported AEs, n (%)	REZUROCK 200 mg QD (n=66)	REZUROCK 200 mg BID (n=66)	Overall (N=132)
All grades in ≥20% of patients			
Fatigue	30 (46)	20 (30)	50 (38)
Diarrhea	23 (35)	21 (32)	44 (33)
Nausea	23 (35)	18 (27)	41 (31)
Cough	20 (30)	17 (26)	37 (28)
Upper respiratory tract infection	17 (26)	18 (27)	35 (27)
Dyspnea	21 (32)	12 (18)	33 (25)
Headache	13 (20)	18 (27)	31 (24)
Peripheral edema	17 (26)	13 (20)	30 (23)
Vomiting	18 (27)	10 (15)	28 (21)
Muscle spasms	13 (20)	13 (20)	26 (20)
Grade ≥3 in ≥5% of patients			
Pneumonia	6 (9)	4 (6)	10 (8)
Hypertension	4 (6)	4 (6)	8 (6)
Hyperglycemia	3 (5)	3 (5)	6 (5)

- AEs were overall consistent with those expected in patients with cGVHD receiving corticosteroids and other immunosuppressants
  - There was 1 reported case of Epstein-Barr virus and 1 reported case of CMV reactivation

Safety overview	REZUROCK 200 mg QD (n=66)	REZUROCK 200 mg BID (n=66)	Overall (N=132)
Median duration of treatment, mo	9.4	11.8	10.4
Any AE, n (%)	65 (99)	66 (100)	131 (99)
Grade ≥3 AEs, n (%)	37 (56)	34 (52)	71 (54)
SAEs, n (%)	27 (41)	23 (35)	50 (38)
Drug-related AEs, n (%)			
Any related AE	49 (74)	40 (61)	89 (67)
Related SAEs	5 (8)	2 (3)	7 (5)
Deaths[a], n (%)	8 (12)	6 (9)	14 (11)

[a]Six subjects died during long-term follow-up (>28 days after the last dose).

According to the Summary of Product Characteristics, the dosage of Rezurock should be increased to 200 mg twice daily when co-administered with strong CYP3A inducers or proton pump inhibitors (PPIs).

AE, adverse event; AML, acute myeloid leukemia; MODS, multiple organ dysfunction syndrome; SAE, serious adverse event.

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Responses with REZUROCK were seen after failure of ≥2 prior lines of therapy[1]

Study design[1]: ROCKstar was a pivotal phase 2, open label, non-controlled, randomized, multicenter study that evaluated the efficacy and safety of REZUROCK in patients with cGvHD after receiving 2 to 5 prior lines of systemic therapy.

Treatment consisted of REZUROCK 200 mg (n=66) and was administered continuously until clinically significant progression of cGvHD or unacceptable toxicity.

Primary end point[1]: Best ORR at any time, defined as the proportion of subjects who achieved CR or PR according to the 2014 NIH cGVHD Consensus Criteria

- **Clinically meaningful** and **statistically significant** ORR of 74% (95% CI, 62-84)[1]
- Responses across **all evaluated organs,** including those with fibrotic manifestations[1,4]
- Median time to response was **4.4 weeks** (3.7-40.6)[3]
- FFS[a] rate at 6 (73%) and 12 (57%) months and estimated OS[b] (84%) rate at **24 months**[1,2]

[a]FFS was defined as the absence of relapse, nonrelapse mortality or a need for additional systemic therapy.[1]
[b]OS was defined as the time from the first dose of REZUROCK to the date of death due to any cause.[2]

ORR, overall response rate; CR, complete response; PR, partial response; FFS, failure free survival; OS, overall survival.

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Prescribing Information: REZUROCK (belumosudil) ▼ 200mg film-coated tablets (Licence valid in GB only)

Therapy should be initiated and supervised by physicians experienced in the management of chronic GVHD.
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each film-coated tablet contains belumosudil mesilate, equivalent to 200mg belumosudil.

Indication: Rezurock is indicated for the treatment of patients aged 12 years and older with chronic graft-versus- host disease (chronic GVHD) who have received at least two prior lines of systemic therapy.

Dosage and Administration: The recommended dose of Rezurock is 200mg administered orally once daily at approximately the same time with a meal. The film-coated tablet should not be broken, crushed or chewed. Treatment should continue until disease progression or unacceptable toxicity. A complete blood cell count and liver function test must be performed before initiating therapy with Rezurock. Perform liver function tests at least monthly throughout treatment. Dose modification due to hepatotoxicity and other adverse reactions: For Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (>5 – 20 × upper limit of normal (ULN)) or Grade 2 bilirubin (>1.5 – 3 × ULN) or other Grade 3 adverse reactions, hold Rezurock until recovery to ≤Grade 1, then resume Rezurock at the recommended dose at physician's discretion. For Grade 4 ALT or AST (>20 × ULN) or Grade ≥3 bilirubin (>3 × ULN) or other Grade 4 adverse reactions, permanently discontinue Rezurock. Dose modification due to drug interactions: *Strong CYP3A Inducers:* Increase the dosage of Rezurock to 200mg twice daily when co-administered with strong CYP3A inducers. *Proton Pump Inhibitors:* Increase the dosage of Rezurock to 200mg twice daily when co- administered with proton pump inhibitors. Delayed or missed dose: If a dose is missed or delayed for <12 hours after the scheduled dose, the dose should be taken as soon as possible on the same day with a return to the normal schedule the following day. If a dose is missed or delayed for >12 hours after the scheduled dose, the dose should be taken at the usual time the following day. If a patient vomits following the intake of a dose, the next dose should be taken at the usual time the following day. Patients should not take extra doses to make up the missed dose.

Special Populations: Hepatic impairment: Dose modification is not recommended when administering belumosudil to patients with mild or moderate hepatic impairment (Child-Pugh A and B). Belumosudil is not recommended in patients with severe hepatic impairment. The safety and efficacy of belumosudil in severe (Child-Pugh C) hepatic impairment has not been evaluated. For patients with pre-existing severe hepatic impairment (Child-Pugh C), consider the risks and potential benefits before initiating treatment with belumosudil. Monitor patients frequently for adverse reactions.

Renal impairment: No dose modification of Rezurock is required in patients with mild or moderate renal impairment (creatine clearance ≥30 mL/min). No data are available for patients with severe renal impairment (creatine clearance<30 mL/min) or for patients with end-stage renal disease on dialysis. Use with caution. Elderly patients (≥65 years): No additional dose adjustments are recommended for elderly patients. Paediatric population: The posology is the same in adults and adolescents aged 12 – 18 years. The safety and efficacy of Rezurock in children and adolescents aged below 12 years of age have not been established. No data are available.

Contraindications: Pregnancy. Hypersensitivity to the active substance or to any of the excipients.

Precautions and Warnings: Female patients of childbearing potential and male patients with female partners of childbearing potential: Women of childbearing potential (WOCBP) should be advised to avoid becoming pregnant while they or their male partner are taking belumosudil and of the potential risk to a fetus. WOCBP should be advised to have a pregnancy test prior to starting treatment with belumosudil. WOCBP and male patients with female partners of childbearing potential must use a highly effective method of contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil. Hepatotoxicity: Increases in liver function tests were observed in clinical studies with belumosudil and generally occurred early during treatment with the incidence decreasing thereafter. Liver function tests should be performed prior to the initiation of treatment with belumosudil and monitored at least monthly during treatment with belumosudil and the dose should be adjusted for ≥Grade 2 toxicities. Sodium: This product is essentially sodium free. **Interactions:** Effect of CYP3A inhibitors on belumosudil: The co-administration of multiple doses of itraconazole did not alter exposure to belumosudil to any clinically relevant extent. Effect of CYP3A inducers on belumosudil: The co- administration of multiple doses of rifampin decreased belumosudil Cmax by 59% and AUC by 72%. The co- administration of strong CYP3A4 inducers with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. The co-administration of moderate CYP3A4 inducers e.g., efavirenz is predicted to have a reduced effect on belumosudil as compared to strong CYP3A4 inducers. The co-administration of moderate CYP3A4 inducers with belumosudil may decrease belumosudil exposure. No dose adjustment is recommended. Effect of proton pump inhibitors on belumosudil: The co-administration of multiple doses of rabeprazole decreased belumosudil Cmax by 87% and AUC by 80%. The co-administration of multiple doses of omeprazole decreased belumosudil Cmax by 68% and AUC by 47%. The co-administration of proton pump inhibitors with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. Effect of other gastric acid reducing agents on belumosudil: The co-administration of belumosudil with gastric acid reducing agents other than proton pump inhibitors may decrease belumosudil exposure. No dose adjustment is recommended, however belumosudil and the gastric acid reducing agent should be taken 12 hours apart. In vitro studies: *Effect of belumosudil on CYP3A substrates:* The co- administration of belumosudil is predicted to increase midazolam Cmax and AUC approximately 1.3- and 1.5-fold, respectively. No dose adjustment is recommended.

The co- administration of belumosudil may increase exposure of sensitive CYP3A4 substrates with a narrow therapeutic index such as ciclosporin and tacrolimus. No dose adjustment is recommended. *Effect of belumosudil on CYP2C9 substrates*: The co-administration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin). *Effect of belumosudil on CYP2C8 substrates*: The co-administration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate. *Effect of belumosudil on UGT1A1 substrates*: Belumosudil is a weak inhibitor of UGT1A1, the clinical consequences are not known. *Transporters*: Belumosudil is a substrate of P-gp. Belumosudil inhibits BCRP, P-gp, and OATP1B1. The co-administration of oral BCRP, P-gp and OATP1B1 substrates with belumosudil may increase the concentrations of the substrate drugs (such as digoxin and docetaxel).

Pregnancy: There are no data on the use of belumosudil in pregnant women. Belumosudil can cause fetal harm based on findings from animal studies and its mechanism of action. As a precautionary measure, belumosudil is contraindicated in pregnancy. **Breast-feeding:** It is unknown whether belumosudil or its metabolites are excreted in human milk. No data are available regarding the presence of belumosudil or its metabolites in animal or human milk or its effects on the breast-fed child, or on milk production. A risk to the infant cannot be excluded. Because of the potential for serious adverse reactions in a breast-fed child, breast-feeding should be discontinued during treatment with belumosudil and for at least one week after the last dose. **Fertility:** There are no human data on the effect of belumosudil on fertility. Based on findings from animal studies, belumosudil may impair male and female fertility at dose levels above the recommended clinical dose. The effects on fertility are reversible.

Adverse Reactions: Very common: Nausea, asthenia. Common: upper and lower respiratory tract infections, anaemia, leukopenia, platelet count decreased, decreased appetite, hyperglycaemia, headache, neuropathy peripheral, dizziness, hypertension, dyspnoea, cough, diarrhoea, vomiting, abdominal pain, constipation, AST and ALT increased, gamma-glutamyltransferase increased, pruritus, musculoskeletal pain, muscle spasms, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine increased, oedema, pyrexia, weight decreased. *Prescribers should consult the SmPC in relation to other adverse reactions.*

Legal Category: POM

GB List Price and Marketing Authorisation Number:
200mg x 30 tablets (PLGB 04425/0902): £6708.

Marketing Authorisation Holder: Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.

Further information is available from: Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.
uk-medicalinformation@sanofi.com

Date of preparation: January 2024

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to the Sanofi drug safety department on Tel: 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com

References:

1. Cutler C, Lee SJ, Arai S, et al; on behalf of the ROCKstar Study Investigators. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. *Blood*. 2021;138(22):2278-2289. doi:10.1182/blood.2021012021
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