REZUROCK™
(belumosudil) tablets

With a different way to treat **cGVHD**,[1-3]

REZUROCK can help patients

ROCK ON

For patients with cGVHD aged ≥12 years after failure of at least 2 prior lines of systemic therapy.[1,4]

cGVHD, chronic graft-versus-host disease.

INDICATION

REZUROCK™ (belumosudil) is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Embryo-Fetal Toxicity:** Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose

Please see additional Important Safety Information throughout.
Please see accompanying full Prescribing Information.

Chronic GVHD presents multiple challenges for HCPs and their patients who have already suffered so much[1,5-7]

Current treatment options may not address the critical aspects of cGVHD, and patients whose initial therapies failed will face further complications[6,8-10]

Immunosuppressive therapy plays an important role in cGVHD; however, it is not always effective and may be associated with a high AE burden.[6,8,10]

Disease progression is frequent and should be aggressively prevented.[6,11]

- More than 70% of patients with cGVHD require additional treatment following initial therapies[10,12]

Multiorgan involvement is common in patients whose disease continues to progress.[4]

- Of patients who received ≥3 lines of systemic therapy, 42% had involvement of ≥4 organs at the time of diagnosis[13]

Addressing fibrosis can be difficult.[10]

- The relationship between inflammation and fibrosis in cGVHD is complex and not fully understood[14,15]
- The significant morbidity and life-threatening complications associated with cGVHD are largely the result of fibrosis[16]
- Although some aspects of inflammation in cGVHD can be addressed, there is limited evidence regarding the effectiveness of current treatments on fibrosis[9,17-21]

Chronic GVHD may have detrimental effects on QOL.[5]

- The burden of cGVHD is multifaceted, with patients experiencing poor QOL and progressive disability[5,22]
- The clinically significant reductions in QOL that can occur with all severity grades (mild through severe) of cGVHD may be underestimated by physicians[5]

There is a need for an immunomodulatory treatment that does not suppress the immune system, providing a different pathway for patients whose initial therapies failed.[2,9]

AE, adverse event; GVHD, graft-versus-host disease; HCP, health care professional; QOL, quality of life.

IMPORTANT SAFETY INFORMATION (cont)

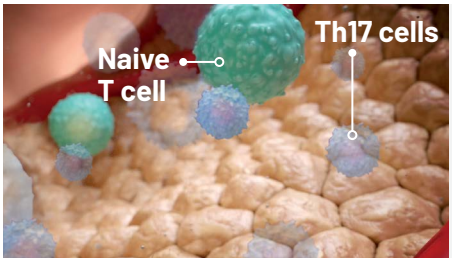
Adverse Reactions

- The most common (≥ 20%) adverse reactions, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension

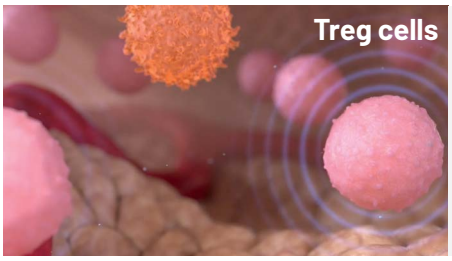
REZUROCK targets both the **inflammatory** and the **fibrotic** processes of cGVHD[1-3]

REZUROCK, a selective ROCK2 inhibitor, is a targeted therapy designed to restore immune homeostasis[1-3]

HOW DOES REZUROCK IMPACT INFLAMMATION?[2,23,24]



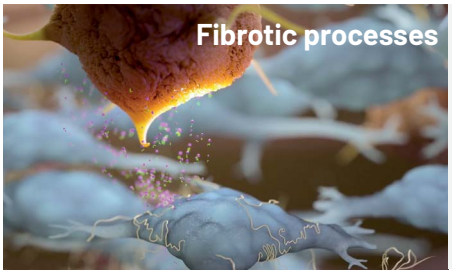
Decreases the activation of STAT3, triggering the significant downregulation of both Th17 and Tfh cells, leading to the decreased production of pro-inflammatory cytokines[2,23]



Increases the phosphorylation of STAT5, causing the upregulation of Treg cells[24]

Reduces inflammation via its immunomodulatory effect on STAT3 and STAT5 phosphorylation[2,23]

HOW DOES REZUROCK IMPACT FIBROSIS?[3,25]



Prevents the polymerization of G-actin to F-actin, as well as MRTF changes to profibrotic gene expression[25]

Downregulates fibrosis, as evidenced by decreased collagen deposition around the bronchioles and the delayed progression of scleroderma in animal cGVHD models[3]

To learn more about the MOA, visit **REZUROCKhcp.com**.

As an oral selective ROCK2 inhibitor, REZUROCK is an effective and innovative treatment designed to restore **immune homeostasis** and to **downregulate the fibrotic processes** of cGVHD.[1-3]

MOA, mechanism of action; MRTF, myocardin-related transcription factor; ROCK2, rho-associated coiled-coil-containing protein kinase-2; STAT3, signal transducer and activator of transcription 3; STAT5, signal transducer and activator of transcription 5; Tfh, follicular helper T [cell]; Th17, type 17 helper T [cell]; Treg, regulatory T [cell].

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REZUROCK was evaluated in the pivotal ROCKstar (KD025-213) study in a **real-world demographic** of patients with cGVHD[1]

Patients received REZUROCK after failure of 2 to 5 previous lines of systemic therapy and were representative of those you see in clinical practice every day[1,26]

SELECT ROCKstar STUDY PATIENT BASELINE CHARACTERISTICS[26]

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
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 (%)[4]	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)
Prior systemic cGVHD therapy type, n (%)	
CS (prednisone)	65 (99)
Tacrolimus	40 (61)
ECP	31 (47)
Sirolimus	29 (44)
Ibrutinib	22 (33)
Ruxolitinib	20 (30)
Cyclosporine	4 (6)
Imatinib	3 (5)

Study design: ROCKstar was a pivotal phase 2, open-label, 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 once daily (n=66) or REZUROCK 200 mg BID (n=66), stratified according to cGVHD severity and prior ibrutinib treatment. REZUROCK was administered continuously until clinically significant progression of cGVHD or unacceptable toxicity.[26]

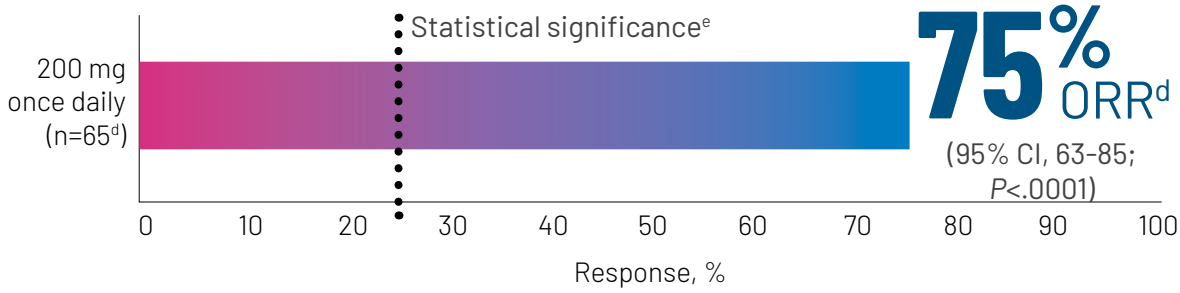
- **Primary end point:** ORR,[b] according to the 2014 NIH cGVHD Consensus Criteria[26]
- **Key secondary end points**[c]: safety, DOR, TTR, LSS score, change in CS/CNI dose, FFS and OS[26]

aGVHD, acute graft-versus-host disease; BID, twice a day; CNI, calcineurin inhibitor; CR, complete response; CS, corticosteroid(s); DOR, duration of response; ECP, extracorporeal photopheresis; FDA, US Food and Drug Administration; FFS, failure-free survival; LSS, Lee Symptom Scale; NIH, National Institutes of Health; ORR, overall response rate; OS, overall survival; PPI, proton pump inhibitor; PR, partial response; TTR, time to response.

[a]The final FDA 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 Prescribing Information, where n=65.
[b]Proportion of patients who achieved CR or PR according to the 2014 NIH cGVHD Consensus Criteria.[26]
[c]Prespecified secondary end point; not powered to show statistical significance.

REZUROCK achieved **clinically meaningful responses** across all patient types[1,26]

STATISTICALLY SIGNIFICANT ORR FOLLOWING TREATMENT WITH REZUROCK 200 mg ONCE DAILY[1,27,28]



[d]Based on a final analysis by the FDA (n=65).
[e]Statistical significance was achieved if the lower bound of the 95% CI of ORR exceeded 30%.[27]

REZUROCK ALSO DEMONSTRATED CLINICALLY MEANINGFUL ORRs ACROSS KEY SUBGROUPS IN THE 200-mg ONCE-DAILY ARM[4]

89%
in patients with an **EARLY[f] cGVHD DIAGNOSIS**
(n/N=32/36)

76%
in patients with **SEVERE cGVHD**
(n/N=35/46)

73%
in patients with **cGVHD INVOLVING ≥4 ORGANS**
(n/N=24/33)

70%
in patients who received **>3 PRIOR LINES OF SYSTEMIC THERAPY**
(n/N=21/30)

75%
in patients who were **REFRACTORY TO THEIR PRIOR LINE OF SYSTEMIC THERAPY**
(n/N=9/12)

73%
in patients who received **PRIOR IBRUTINIB THERAPY**
(n/N=16/22)

65%
in patients who received **PRIOR RUXOLITINIB THERAPY**
(n/N=13/20)

[f]Early diagnosis was defined as <28 months from time of initial diagnosis to enrollment.[4]

IMPORTANT SAFETY INFORMATION (cont)

Adverse Reactions (cont)

- Permanent discontinuation of REZUROCK due to adverse reactions occurred in 18% of patients. The adverse reactions which resulted in permanent discontinuation of REZUROCK in > 3% of patients included nausea (4%). Adverse reactions leading to dose interruption occurred in 29% of patients. The adverse reactions leading to dose interruption in ≥ 2% were infections (11%), diarrhea (4%), and asthenia, dyspnea, hemorrhage, hypotension, liver function test abnormal, nausea, pyrexia, edema, and renal failure with (2% each)

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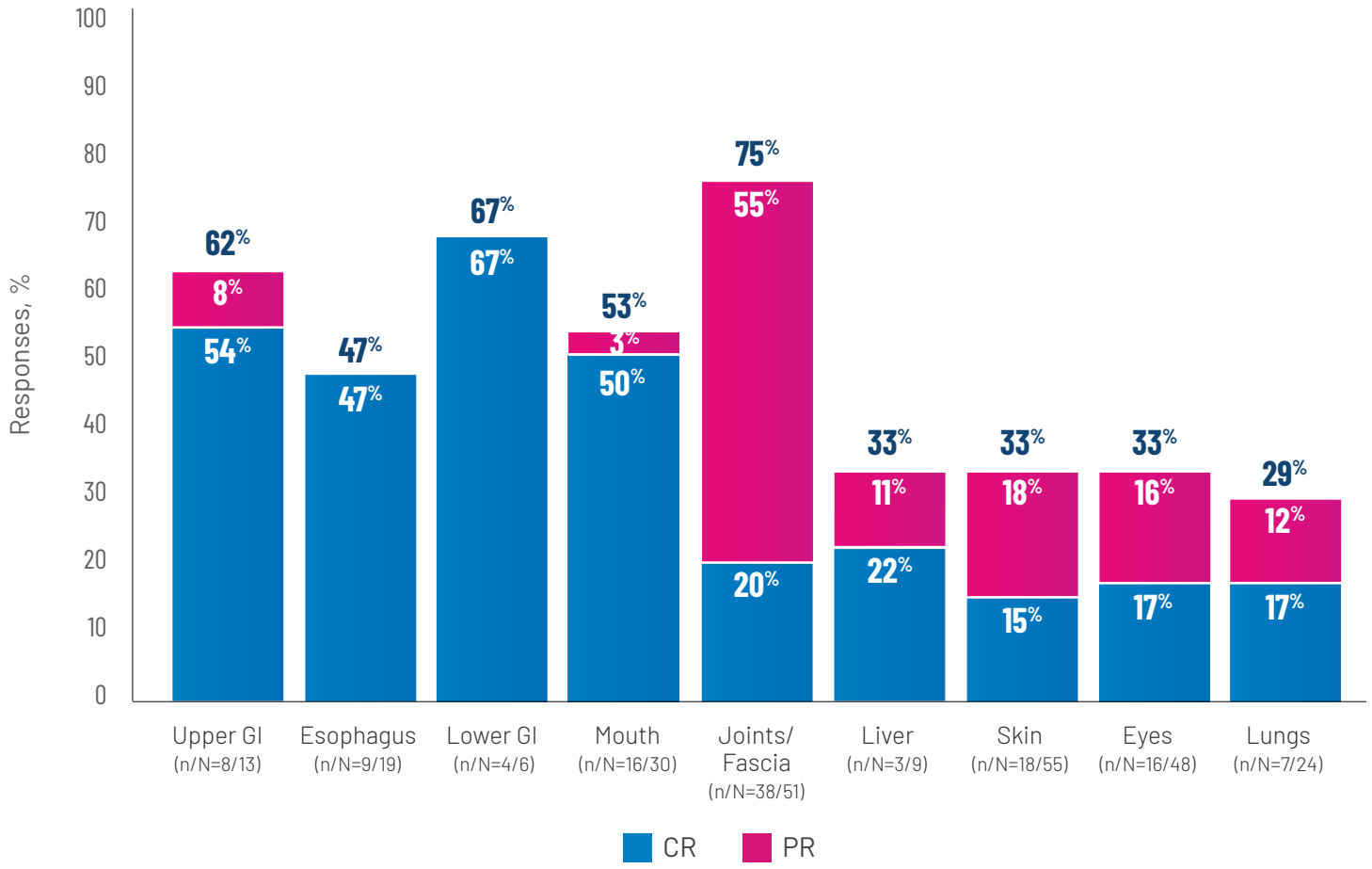
Responses were **achieved across all affected organs** evaluated in the ROCKstar study[26]

CR was observed in all organs, including those with fibrotic manifestations, such as the lungs, skin and eyes[26]

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



Responses in the lungs are notable, given that advanced fibrotic changes can be irreversible.[29]

GI, gastrointestinal; mITT, modified intent-to-treat.

IMPORTANT SAFETY INFORMATION (cont)

Adverse Reactions (cont)

- Monitor total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at least monthly

Drug Interactions

- **Strong CYP3A Inducers:** Coadministration of REZUROCK with strong CYP3A inducers decreases belumosudil exposure, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with strong CYP3A inducers

REZUROCK provided a **sustained response** in many patients with cGVHD[26]

4
WEEKS

The **time to response** was as early as 4 weeks.[26]

63%
OF RESPONSES

were observed between **weeks 4 and 8** with REZUROCK 200 mg once daily in the responder population.[4,a]

94%
OF RESPONSES

were observed by **week 24** with REZUROCK 200 mg once daily in the responder population.[4,a]

Approximately
61%
OF RESPONDERS[a]

demonstrated a **sustained response** for ≥20 weeks.[4]

62%
OF THE RESPONDER POPULATION[b]

There was **no death or new systemic therapy initiation** in 62% (95% CI, 46-74) of the responder population at 12 months.[1]

[a]The responder population in the 200-mg once-daily arm was n=49.[4]
[b]Based on a final analysis by the FDA (n=65).

IMPORTANT SAFETY INFORMATION (cont)

Drug Interactions (cont)

- **Proton Pump Inhibitors:** Coadministration of REZUROCK with proton pump inhibitors decreases belumosudil exposure, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with proton pump inhibitors

Use in Specific Populations

- **Pregnancy:** Based on findings from animal studies and the mechanism of action, REZUROCK can cause fetal harm when administered to pregnant women. There are no available human data on REZUROCK use in pregnant women to evaluate for a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to the fetus

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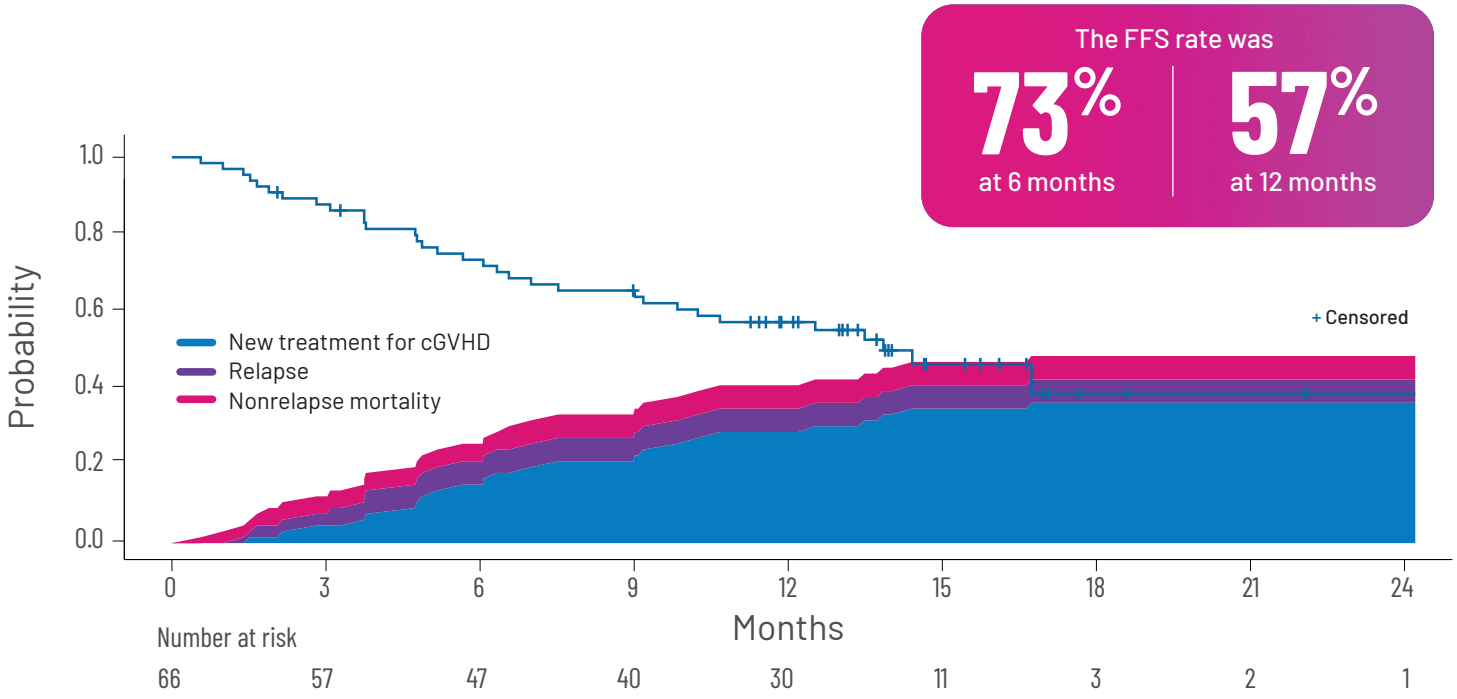
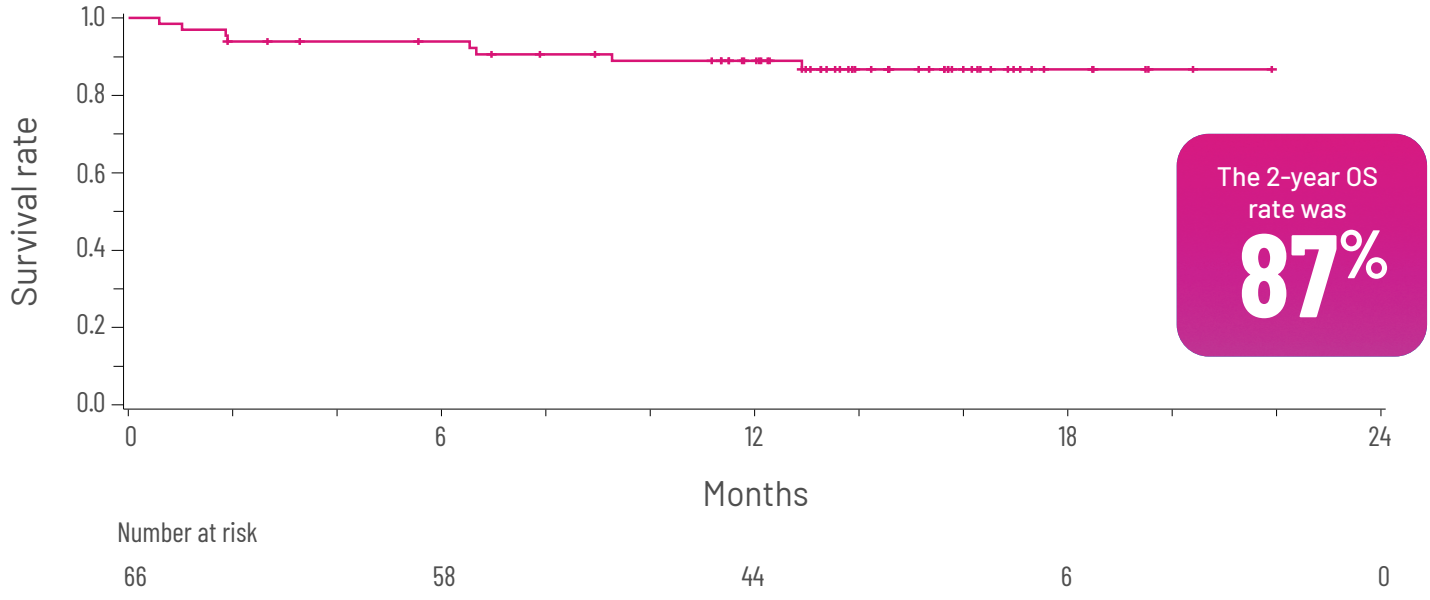
Clinically significant FFS and OS rates with REZUROCK in the pivotal study of patients with cGVHD[4]

FFS[a] WITH REZUROCK 200 mg ONCE DAILY IN THE mITT POPULATION[4]



[a]FFS was defined as the absence of relapse, nonrelapse mortality or a need for additional systemic therapy.[26]

OS[b] WITH REZUROCK 200 mg ONCE DAILY IN THE mITT POPULATION[4]



[b]OS was defined as the time from the first dose of REZUROCK to the date of death due to any cause.[4]

REZUROCK improved QOL scores and reduced dependence on CS and CNI therapies[26]

52%
OF PATIENTS[c]
(95% CI, 40-65)

CLINICALLY MEANINGFUL IMPROVEMENT IN PATIENT-REPORTED QOL[1]

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

[c]Based on a final analysis by the FDA (n=65).

[d]The 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.[30]

REZUROCK REDUCED THE NEED FOR CS AND CNI THERAPIES[4,26]

Dose reductions and discontinuations in patients who received CS therapy[26]	Dose reductions and discontinuations in patients who received CNI therapy[4]
64% of patients (n=42) in the 200-mg once-daily arm **REDUCED THEIR CS DOSES**. The mean percentage change in CS dose reduction was **43%** (n=63) in the mITT population who received REZUROCK 200 mg once daily (**49%** [n=48] in responders and **22%** [n=15] in nonresponders).[e]	**42%** of patients (n=10) in the 200-mg once-daily arm **REDUCED THEIR CNI DOSES**.
20% of patients (n=13) in the 200-mg once-daily arm **DISCONTINUED CS THERAPY**.	**17%** of patients (n=4) in the 200-mg once-daily arm **DISCONTINUED CNI THERAPY**.

[e]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.[27]

IMPORTANT SAFETY INFORMATION (cont)

Use in Specific Populations (cont)

- **Lactation:** There are no data available on the presence of belumosudil or its metabolites in human milk or the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions from belumosudil in the breastfed child, advise lactating women not to breastfeed during treatment with REZUROCK and for at least one week after the last dose

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REZUROCK was well tolerated in patients with cGVHD[4,31]

Safety was evaluated across 2 clinical studies,[a] with the results pooled for analysis[1]

Consider the safety profile of REZUROCK in patients with cGVHD who often receive immunosuppressive therapy.

- There were no reports of CMV infection in both the ROCKstar and the foundational, dose-finding KD025-208 studies, and only 1 report of CMV reactivation in total[26,31]
- There was a low rate of serious (grade ≥3) cytopenias across the total REZUROCK clinical studies population[4,31]
  - In the ROCKstar and KD025-208 clinical studies of REZUROCK, grade ≥3 cytopenias were reported in <4% and 4% of patients, respectively
- The most common (≥20%) adverse reactions, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased and hypertension[1]

MOST PATIENTS WERE ABLE TO MAINTAIN TREATMENT WITH REZUROCK 200 mg ONCE DAILY (n=83)[a] FOR A SUSTAINED PERIOD[4]

9.2
MONTHS

Patients had a median duration of treatment of 9.2 months (range, 0.5-44.7 months).

CMV, cytomegalovirus.

[a] Data included results from a dose-finding multicenter study of REZUROCK for the treatment of patients with cGVHD (N=54) who had received 1 to 3 prior lines of systemic therapy and required additional treatment. REZUROCK was administered by mouth at 200 mg once daily, 200 mg BID or 400 mg once daily.[31]

IMPORTANT SAFETY INFORMATION (cont)

Use in Specific Populations (cont)

- **Pediatric Use:** The safety and effectiveness of REZUROCK have been established in pediatric patients 12 years and older. The safety and effectiveness of REZUROCK in pediatric patients less than 12 years old have not been established
- **Geriatric Use:** Of the 186 patients with chronic GVHD in clinical studies of REZUROCK, 26% were 65 years and older. No clinically meaningful differences in safety or effectiveness of REZUROCK were observed in comparison to younger patients

Well-established safety profile[1,26,31]

NONLABORATORY ADVERSE REACTIONS IN ≥10% OF PATIENTS WITH cGVHD TREATED WITH REZUROCK 200 mg ONCE DAILY (n=83)[1,a,b]

	All grades, %	Grades 3-4, %
Infections and infestations		
Infection (pathogen not specified)	53	16
Viral infection	19	4
Bacterial infection	16	4
General disorders and administration site conditions		
Asthenia	46	4
Edema	27	1
Pyrexia	18	1
Gastrointestinal		
Nausea	42	4
Diarrhea	35	5
Abdominal pain	22	1
Dysphagia	16	0
Respiratory, thoracic and mediastinal		
Dyspnea	33	5
Cough	30	0
Nasal congestion	12	0
Vascular		
Hemorrhage	23	5
Hypertension	21	7
Musculoskeletal and connective tissue		
Musculoskeletal pain	22	4
Muscle spasm	17	0
Arthralgia	15	2
Nervous system		
Headache	21	0
Metabolism and nutrition		
Decreased appetite	17	1
Skin and subcutaneous		
Rash	12	0
Pruritus	11	0

[b]Please see Table 2 of the REZUROCK Prescribing Information for complete details on nonlaboratory adverse reactions.

Please see additional Important Safety Information throughout.
Please see accompanying full Prescribing Information.

REZUROCK™
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REZUROCK: A once-daily oral tablet for patients with cGVHD[1]

The recommended dose of REZUROCK is 200 mg once daily administered orally[1]

Advise patients to take REZUROCK at approximately the **same time each day** with a meal.

If the patient misses a dose of REZUROCK, instruct the patient **not to take extra doses** to make up for the missed dose.

Inform patients that the REZUROCK tablets should be swallowed whole with a glass of water **without cutting, crushing or chewing the tablets**.

Monitor total bilirubin, AST and ALT at least monthly (see full Prescribing Information for more details, including dose modifications for REZUROCK for adverse reactions).

Recommended dose adjustments for drug interactions[1]

- **Strong CYP3A inducers:** Increase the dosage of REZUROCK to 200 mg BID when coadministered with strong CYP3A inducers
- **Proton pump inhibitors:** Increase the dosage of REZUROCK to 200 mg BID when coadministered with PPIs

ALT, alanine aminotransaminase; AST, aspartate aminotransferase.

Each pale-yellow oblong 200-mg tablet is debossed with "KDM" on one side and "200" on the other side.[1]

Not actual size.

REZUROCK should be dispensed to the patient in the original container only.[1]

IMPORTANT SAFETY INFORMATION (cont)

Use in Specific Populations (cont)

- **Renal and Hepatic Impairment:** Treatment with REZUROCK has not been studied in patients with pre-existing severe renal or hepatic impairment. For patients with pre-existing severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with REZUROCK

You are encouraged to report side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088. You may also contact Kadmon Pharmaceuticals, LLC, at 1-877-377-7862 to report side effects.

INDICATION

REZUROCK™ (belumosudil) is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

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REZUROCK™
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Kadmon is committed to helping support your patients with cGVHD throughout their treatment journey with REZUROCK

Kadmon ASSIST™

Enroll your patients with cGVHD into Kadmon ASSIST (Access, Support System and Insurance Services for Treatment) so our specialists can find the best program to fit your patients' coverage

INSURANCE

Navigating coverage and providing insurance assistance

ACCESS

Providing a free 30-day supply of REZUROCK to eligible patients who experience delays or gaps in their insurance coverage

CO-PAY SAVINGS

Providing commercial co-pay savings for REZUROCK

EDUCATION

Connecting with nurses regarding disease management and treatment with REZUROCK

To enroll patients in Kadmon ASSIST, visit **KadmonASSIST.com** or call **1- 844-KADMON1 (523-6661)**.

REZUROCK is available through our network of authorized **specialty pharmacies and specialty distributors**

Contact any of the authorized specialty pharmacies below to help get your patients started on REZUROCK.

Amber Specialty Pharmacy
Phone: 1-888-370-1724
Fax: 1-402-896-3774
amberpharmacy.com

Biologics by McKesson
Phone: 1-800-850-4306
Fax: 1-800-823-4506
biologics.mckesson.com

Onco360 Oncology Pharmacy
Phone: 1-877-662-6633
Fax: 1-877-662-6355
onco360.com

Contact any of the authorized specialty distributors below to order REZUROCK for your account.

PHYSICIAN DISPENSING OFFICES

Cardinal Health™ Specialty Pharmaceutical Distribution
Phone: 1-877-453-3972
Fax: 1-877-274-9897
specialtyonline.cardinalhealth.com

McKesson Specialty Health
Phone: 1-800-482-6700
Fax: 1-800-289-9285
mscs.mckesson.com

Oncology Supply®
Phone: 1-800-633-7555
Fax: 1-800-248-8205
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INSTITUTIONS/HOSPITALS

ASD Healthcare®
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Fax: 1-800-547-9413
asdhealthcare.com

Cardinal Health™ Specialty Pharmaceutical Distribution
Phone: 1-855-855-0708
Fax: 1-877-274-9897
orderexpress.cardinalhealth.com

McKesson Plasma and Biologics
Phone: 1-877-625-2566
Fax: 1-888-752-7626
connect.mckesson.com

If you need assistance prescribing or ordering REZUROCK, our Kadmon ASSIST team is available to help you **Monday through Friday, 8 AM-8 PM ET, at 1-844-KADMON1 (523-6661)**.

Please see Important Safety Information throughout.
Please see accompanying full Prescribing Information.

REZUROCK™
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Help patients with **cGVHD**

ROCK ON with REZUROCK

- **Targets both inflammation and fibrosis** through selective ROCK2 inhibition[1-3]
- **Clinically and statistically significant efficacy, 75% ORR,**[a] with the 200-mg once-daily dose in a **real-world demographic** of patients with cGVHD[1]
- **CR was observed in all organs**, including those with fibrotic manifestations[26]
- There was **no death or new systemic therapy initiation in 62%** (95% CI, 46-74) of the responder population[a] at 12 months[1]
- **Clinically meaningful improvements in QOL**, with **CS and CNI dose reductions and discontinuations** achieved in both responders and nonresponders[26]
- **Well tolerated**[1]
- **Kadmon ASSIST™ patient support services** are available to help eligible patients start and stay on therapy

[a]Based on a final analysis by the FDA (n=65).

Visit **REZUROCKhcp.com** to get your patients started on REZUROCK.

References: 1. REZUROCK. Package insert. Kadmon Pharmaceuticals, LLC; 2021. **2.** Zanin-Zhorov A, Weiss JM, Nyuydzefe MS, et al. Selective oral ROCK2 inhibitor down-regulates IL-21 and IL-17 secretion in human T cells via STAT3-dependent mechanism. *Proc Natl Acad Sci USA*. 2014;111(47):16814-16819. doi:10.1073/pnas.1414189111 **3.** Flynn R, Paz K, Du J, et al. Targeted rho-associated kinase 2 inhibition suppresses murine and human chronic GVHD through a Stat3-dependent mechanism. *Blood*. 2016;127(17):2144-2154. doi:10.1182/blood-2015-10-678706 **4.** Data on file 1. Kadmon Pharmaceuticals, LLC; 2021. **5.** Kurosawa S, Oshima K, Yamaguchi T, et al. Quality of life after allogeneic hematopoietic cell transplantation according to affected organ and severity of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2017;23(10):1749-1758. doi:10.1016/j.bbmt.2017.06.011 **6.** Lee SJ, Nguyen TD, Onstad L, et al. 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IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Embryo-Fetal Toxicity:** Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose

Please see additional Important Safety Information throughout.
Please see accompanying full Prescribing Information.

Kadmon

KAD25000214 08/21

REZUROCK™
(belumosudil) tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REZUROCK safely and effectively. See full prescribing information for REZUROCK.

REZUROCK™ (belumosudil) tablets, for oral use
Initial U.S. Approval: 2021

---------- INDICATIONS AND USAGE ----------
REZUROCK is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy. (1)

----------DOSAGE AND ADMINISTRATION ----------
Recommended Dosage: 200 mg taken orally once daily with food. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablet: 200 mg. (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.1, 8.1, 8.3)

---------- DRUG INTERACTIONS ----------
Strong CYP3A Inducers: Increase REZUROCK dosage to 200 mg twice daily. (7.1)
Proton Pump Inhibitors: Increase REZUROCK dosage to 200 mg twice daily. (7.1)

---------- ADVERSE REACTIONS ----------
The most common (≥ 20%) adverse reactions, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kadmon Pharmaceuticals, LLC at 1-877-377-7862 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

REZUROCK is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of REZUROCK is 200 mg given orally once daily until progression of chronic GVHD that requires new systemic therapy.

Instruct the patient on the following:

- Swallow REZUROCK tablets whole. Do not cut, crush, or chew tablets.
- Take REZUROCK with a meal at approximately the same time each day *[see Clinical Pharmacology (12.3)]*.
- If a dose of REZUROCK is missed, instruct the patient to not take extra doses to make up the missed dose.

Treatment with REZUROCK has not been studied in patients with pre-existing severe renal or hepatic impairment. For patients with pre-existing severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with REZUROCK *[see Clinical Pharmacology (12.3)]*.

2.2 Dose Modifications for Adverse Reactions

Monitor total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at least monthly.

Modify the REZUROCK dosage for adverse reactions as per **Table 1**.

Table 1: Recommended Dosage Modifications for REZUROCK for Adverse Reactions

Adverse Reaction	**Severity***	**REZUROCK Dosage Modifications**
Hepatotoxicity *[see Adverse Reactions (6.1)]*	Grade 3 AST or ALT (5x to 20x ULN) or Grade 2 bilirubin (1.5x to 3x ULN)	Hold REZUROCK until recovery of bilirubin, AST and ALT to Grade 0-1, then resume REZUROCK at the recommended dose.
	Grade 4 AST or ALT (more than 20x ULN) or Grade ≥ 3 bilirubin (more than 3x ULN)	Discontinue REZUROCK permanently.
Other adverse reactions *[see Adverse Reactions (6.1)]*	Grade 3	Hold REZUROCK until recovery to Grade 0-1, then resume REZUROCK at the recommended dose level.
	Grade 4	Discontinue REZUROCK permanently.

*Based on CTCAE v 4.03

2.3 Dosage Modification Due to Drug Interactions

Strong CYP3A Inducers

Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with strong CYP3A inducers *[see Drug Interactions (7.1)]*.

Proton Pump Inhibitors

Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with proton pump inhibitors *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Each 200 mg tablet is a pale yellow film-coated oblong tablet debossed with "KDM" on one side and "200" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of belumosudil to pregnant rats and rabbits during the period organogenesis caused adverse developmental outcomes including embryo-fetal mortality and malformations at maternal exposures (AUC) less than those in patients at the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely variable conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Chronic Graft versus Host Disease

In two clinical trials (Study KD025-213 and Study KD025-208), 83 adult patients with chronic GVHD were treated with REZUROCK 200 mg once daily *[see Clinical Studies (14.1)]*. The median duration of treatment was 9.2 months (range 0.5 to 44.7 months).

Fatal adverse reaction was reported in one patient with severe nausea, vomiting, diarrhea and multi-organ failure.

Permanent discontinuation of REZUROCK due to adverse reactions occurred in 18% of patients. The adverse reactions which resulted in permanent discontinuation of REZUROCK in > 3% of patients included nausea (4%). Adverse reactions leading to dose interruption occurred in 29% of patients. The adverse reactions leading to dose interruption in ≥ 2% were infections (11%), diarrhea (4%), and asthenia, dyspnea, hemorrhage, hypotension, liver function test abnormal, nausea, pyrexia, edema, and renal failure with (2% each).

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension.

Table 2 summarizes the nonlaboratory adverse reactions.

Table 2: Nonlaboratory Adverse Reactions in ≥ 10% Patients with Chronic GVHD Treated with REZUROCK

Adverse Reaction	REZUROCK 200 mg once daily (N=83)	
	All Grades (%)	Grades 3-4 (%)
Infections and infestations		
Infection (pathogen not specified)[a]	53	16
Viral infection[b]	19	4
Bacterial infection[c]	16	4
General disorders and administration site conditions		
Asthenia[d]	46	4
Edema[e]	27	1
Pyrexia	18	1
Gastrointestinal		
Nausea[f]	42	4
Diarrhea	35	5
Abdominal pain[g]	22	1
Dysphagia	16	0
Respiratory, thoracic and mediastinal		
Dyspnea[h]	33	5
Cough[i]	30	0
Nasal congestion	12	0
Vascular		
Hemorrhage[j]	23	5
Hypertension	21	7
Musculoskeletal and connective tissue		
Musculoskeletal pain[k]	22	4

Adverse Reaction	REZUROCK 200 mg once daily (N=83)	
	All Grades (%)	Grades 3-4 (%)
Muscle spasm	17	0
Arthralgia	15	2
Nervous system		
Headache[l]	21	0
Metabolism and nutrition		
Decreased appetite	17	1
Skin and subcutaneous		
Rash[m]	12	0
Pruritus[n]	11	0

[a] infection with an unspecified pathogen includes acute sinusitis, device related infection, ear infection, folliculitis, gastroenteritis, gastrointestinal infection, hordeolum, infectious colitis, lung infection, skin infection, tooth infection, urinary tract infection, wound infection, upper respiratory tract infection, pneumonia, conjunctivitis, sinusitis, respiratory tract infection, bronchitis, sepsis, septic shock.

[b] includes influenza, rhinovirus infection, gastroenteritis viral, viral upper respiratory tract infection, bronchitis viral, Epstein-Barr viremia, Epstein-Barr virus infection, parainfluenzae virus infection, Varicella zoster virus infection, viral infection.

[c] includes cellulitis, Helicobacter infection, Staphylococcal bacteremia, catheter site cellulitis, Clostridium difficile colitis, Escherichia urinary tract infection, gastroenteritis Escherichia coli, Pseudomonas infection, urinary tract infection bacterial.

[d] includes fatigue, asthenia, malaise.

[e] includes edema peripheral, generalized edema, face edema, localized edema, edema.

[f] includes nausea, vomiting.

[g] includes abdominal pain, abdominal pain upper, abdominal pain lower.

[h] includes dyspnea, dyspnea exertional, apnea, orthopnea, sleep apnea syndrome.

[i] includes cough, productive cough.

[j] includes contusion, hematoma, epistaxis, increased tendency to bruise, conjunctival hemorrhage, hematochezia, mouth hemorrhage, catheter site hemorrhage, hematuria, hemothorax, purpura.

[k] includes pain in extremity, back pain, flank pain, limb discomfort, musculoskeletal chest pain, neck pain, musculoskeletal pain.

[l] includes headache, migraine.

[m] includes rash, rash maculo-papular, rash erythematous, rash generalized, dermatitis exfoliative.

[n] includes pruritus, pruritus generalized.

Table 3 summarizes the laboratory abnormalities in REZUROCK.

Table 3: Selected Laboratory Abnormalities in Patients with Chronic GVHD Treated with REZUROCK

	REZUROCK 200 mg once daily		
	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	**(N)**	**(%)**	**(%)**
Chemistry			
Phosphate Decreased	76	28	7
Gamma Glutamyl Transferase Increased	47	21	11
Calcium Decreased	82	12	1
Alkaline Phosphatase Increased	80	9	0
Potassium Increased	82	7	1
Alanine Aminotransferase Increased	83	7	2
Creatinine Increased	83	4	0
Hematology			
Lymphocytes Decreased	62	29	13
Hemoglobin Decreased	79	11	1
Platelets Decreased	82	10	5
Neutrophil Count Decreased	83	8	4

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on REZUROCK

Strong CYP3A Inducers

Coadministration of REZUROCK with strong CYP3A inducers decreases belumosudil exposure *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK when coadministered with strong CYP3A inducers *[see Dosage and Administration (2.3)]*.

Proton Pump Inhibitors

Coadministration of REZUROCK with proton pump inhibitors decreases belumosudil exposure *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK when coadministered with proton pump inhibitors *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action *[see Clinical Pharmacology (12.1)]*, REZUROCK can cause fetal harm when administered to pregnant women. There are no available human data on REZUROCK use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of belumosudil to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and embryo-fetal malformations at maternal exposures (AUC) approximately ≥ 3- (rat) and ≥ 0.07 (rabbit) times the human exposure (AUC) at the recommended dose (see Animal Data). Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Embryo-fetal development studies were conducted in rats with administration of belumosudil to pregnant animals during the period of organogenesis at oral doses of 25, 50, 150, and 300 mg/kg/day in a pilot study and doses of 15, 50, and 150 mg/kg/day in a pivotal study. In the pilot study, maternal toxicity and embryo-fetal developmental effects were observed. Maternal toxicity (reduced body weight gain) occurred at 150 and 300 mg/kg/day doses. Increased post-implantation loss occurred at 50 and 300 mg/kg/day. Fetal-malformations were observed at ≥ 50 mg/kg/day and included absence of anus and tail, omphalocele, and dome shaped head. The exposure (AUC) at 50 mg/kg/day in rats is approximately 3 times the human exposure at the recommended dose of 200 mg.

In an embryo-fetal developmental study in rabbits, pregnant animals administered oral doses of belumosudil at 50, 125, and 225 mg/kg/day during the period of organogenesis resulted in maternal toxicity and embryo-fetal developmental effects. Maternal toxicity (body weight loss and mortality) was observed at doses ≥ 125 mg/kg/day. Embryo-fetal effects were observed at doses ≥ 50 mg/kg/day and included spontaneous abortion, increased post-implantation loss, decreased percentage of live fetuses, malformations, and decreased fetal body weight. Malformations included those in the tail (short), ribs (branched, fused or deformed), sternebrae (fused), and neural arches (fused, misaligned, and deformed). The exposure (AUC) at 50 mg/kg/day in rabbits is approximately 0.07 times the human exposure at the recommended dose of 200 mg.

8.2 Lactation

Risk Summary

There are no data available on the presence of belumosudil or its metabolites in human milk or the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions from belumosudil in the breastfed child, advise lactating women not to breastfeed during treatment with REZUROCK and for at least one week after the last dose.

8.3 Females and Males of Reproductive Potential

REZUROCK can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

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

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose of REZUROCK. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose of REZUROCK.

Infertility

Females

Based on findings from rats, REZUROCK may impair female fertility. The effect on fertility is reversible *[see Nonclinical Toxicology (13.1)]*.

Males

Based on findings from rats and dogs, REZUROCK may impair male fertility. The effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of REZUROCK have been established in pediatric patients 12 years and older. Use of REZUROCK in this age group is supported by evidence from adequate and well-controlled studies of REZUROCK in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of drug substance, that the exposure of drug substance is expected to be similar between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients.

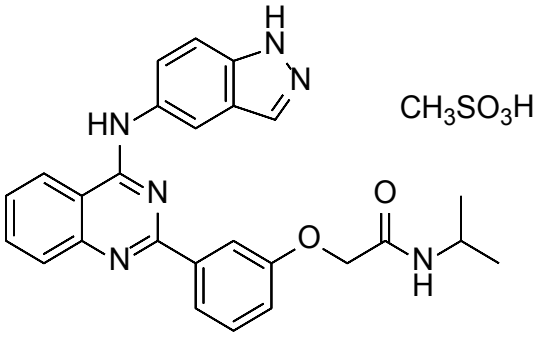
The safety and effectiveness of REZUROCK in pediatric patients less than 12 years old have not been established.

8.5 Geriatric Use

Of the 186 patients with chronic GVHD in clinical studies of REZUROCK, 26% were 65 years and older. No clinically meaningful differences in safety or effectiveness of REZUROCK were observed in comparison to younger patients.

11 DESCRIPTION

Belumosudil is a kinase inhibitor. The active pharmaceutical ingredient is belumosudil mesylate with the molecular formula $C_{27}H_{28}N_6O_5S$ and the molecular weight is 548.62 g/mol. The chemical name for belumosudil mesylate is 2-{3-[4-(1*H*-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-*N*-(propan-2-yl) acetamide methanesulfonate (1:1). The chemical structure is as follows:



Belumosudil mesylate is a yellow powder that is practically insoluble in water, slightly soluble in methanol and DMF and soluble in DMSO.

REZUROCK tablets are for oral administration. Each tablet contains 200 mg of the free base equivalent to 242.5 mg of belumosudil mesylate. The tablet also contains the following inactive ingredients: microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

The tablet film consists of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Belumosudil is an inhibitor of rho-associated, coiled-coil containing protein kinase (ROCK) which inhibits ROCK2 and ROCK1 with IC_{50} values of approximately 100 nM and 3 µM, respectively. Belumosudil down-regulated proinflammatory responses via regulation of STAT3/STAT5 phosphorylation and shifting Th17/Treg balance in ex-vivo or in vitro-human T cell assays. Belumosudil also inhibited aberrant pro-fibrotic signaling, in vitro. In vivo, belumosudil demonstrated activity in animal models of chronic GVHD.

12.2 Pharmacodynamics

Belumosudil exposure-response relationships and the time course of pharmacodynamic response are not established.

12.3 Pharmacokinetics

The following pharmacokinetic parameters are presented for chronic GVHD patients administered belumosudil 200 mg once daily, unless otherwise specified. The mean (% coefficient of variation, %CV) steady-state AUC and C_{max} of belumosudil was 22700 (48%) h•ng/mL and 2390 (44%) ng/mL, respectively. Belumosudil C_{max} and AUC increased in an approximately proportional manner over a dosage range of 200 and 400 mg (1 to 2 times once daily recommended dosage). The accumulation ratio of belumosudil was 1.4.

Absorption

Median T_{max} of belumosudil at steady state was 1.26 to 2.53 hours following administration of 200 mg once daily or twice daily in patients. The mean (%CV) bioavailability was 64% (17%) following a single belumosudil dose in healthy subjects.

Effect of Food

Belumosudil C_{max} and AUC increased 2.2 times and 2 times, respectively, following administration of a single belumosudil dose with a high-fat and high-calorie meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) compared to the fasted state in healthy subjects. Median T_{max} was delayed 0.5 hours.

Distribution

The geometric mean volume of distribution after a single dose of belumosudil in healthy subjects was 184 L (geo CV% 67.7%).

Belumosudil binding to human serum albumin and human α_1-acid glycoprotein was 99.9% and 98.6%, respectively, in vitro.

Elimination

The mean (%CV) elimination half-life of belumosudil was 19 hours (39%), and clearance was 9.83 L/hours (46%) in patients.

Metabolism

Belumosudil is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C8, CYP2D6, and UGT1A9, in vitro.

Excretion

Following a single oral dose of radiolabeled belumosudil in healthy subjects, 85% of radioactivity was recovered in feces (30% as unchanged) and less than 5% in urine.

Specific Populations

No clinically significant differences in belumosudil pharmacokinetics were observed with regard to age (18 to 77 years), sex, weight (38.6 to 143 kg), or mild to moderate renal impairment (eGFR $\geq$ 60 and < 90 mL/min/1.72m^2 to eGFR $\geq$ 30 and < 60 mL/min/1.72m^2). The effect of severe renal impairment on the pharmacokinetics of belumosudil has not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effects of Other Drugs on Belumosudil

Strong Cytochrome P450 (CYP) 3A Inhibitors: There was no clinically meaningful effect on belumosudil exposure when coadministered with itraconazole in healthy subjects.

Strong CYP3A Inducers: Coadministration of rifampin decreased belumosudil C_{max} by 59% and AUC by 72% in healthy subjects.

Moderate CYP3A Inducers: Coadministration of efavirenz is predicted to decrease belumosudil C_{max} by 32% and AUC by 35% in healthy subjects.

Proton Pump Inhibitors: Coadministration of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%, and omeprazole decreased belumosudil C_{max} by 68% and AUC by 47% in healthy subjects.

Effects of Belumosudil on Other Drugs

CYP3A Substrates: Coadministration of belumosudil is predicted to increase midazolam (a sensitive CYP3A substrate) C_{max} and AUC approximately 1.3- and 1.5-fold, respectively.

CYP2C9 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin).

CYP2C8 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate.

In Vitro Studies

Transporter Systems: Belumosudil is a substrate of P-gp. Belumosudil inhibits BCRP, P-gp, and OATP1B1 at clinically relevant concentrations.

Enzymes Systems: Belumosudil is an inhibitor of CYP1A2, CYP2C19, CYP2D6, UGT1A1 and UGT1A9.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with belumosudil.

Belumosudil was not genotoxic in an in vitro bacterial mutagenicity (Ames) assay, in vitro chromosome aberration assay in human peripheral blood lymphocytes (HPBL) or an in vivo rat bone marrow micronucleus assay.

In a combined male and female rat fertility study, belumosudil-treated male animals were mated with untreated females, or untreated males were mated with belumosudil-treated females. Belumosudil was administered orally at doses of 50, 150 or 275 mg/kg/day to male rats 70 days prior to and throughout the mating period, and to female rats 14 days prior to mating and up to Gestation Day 7. At the dose of 275 mg/kg/day, adverse findings in female rats (treated with belumosudil or untreated but mated with treated males) included increased pre- or post-implantation loss and decreased number of viable embryos. Administration of belumosudil to male rats at a dose of 275 mg/kg/day resulted in abnormal sperm findings (reduced motility, reduced count, and increased percentage of abnormal sperm), and testes/epididymis organ changes (reduced weight and degeneration). Fertility was reduced in both treated males or females at the 275 mg/kg/day dose and reached statistical significance in males. Adverse changes in male and female reproductive organs also occurred in general toxicology studies; findings included spermatozoa degeneration at a belumosudil dose of 35 mg/kg/day in dogs and decreased follicular development in ovaries at 275 mg/kg/day in rats. Changes were partially or fully reversed during the recovery period. The exposure (AUC) at the doses of 35 mg/kg/day in dogs, and 275 mg/kg/day in rats is 0.5 times and 8-9 times, respectively, the clinical exposure at the recommended dose of 200 mg daily.

14 CLINICAL STUDIES

14.1 Chronic Graft versus Host Disease

Study KD025-213 (NCT03640481) was a randomized, open-label, multicenter study of REZUROCK for treatment of patients with chronic GVHD who had received 2 to 5 prior lines of systemic therapy and required additional treatment. Patients were excluded from the studies if platelets were < 50 × 10^9/L; absolute neutrophil count < 1.5 × 10^9/L; AST or ALT > 3 × ULN; total bilirubin > 1.5 × ULN; QTc(F) > 480 ms; eGFR < 30 mL/min/1.73 m^2; or FEV1 ≤ 39%. There were 66 patients treated with REZUROCK 200 mg taken orally once daily. Concomitant treatment with supportive care therapies for chronic GVHD was permitted. Concomitant treatment with GVHD prophylaxis and standard care systemic chronic GVHD therapies was permitted as long as the subject has been on a stable dose for at least 2 weeks prior to study. Initiation of new systemic chronic GVHD therapy while on study was not permitted.

Demographics and baseline characteristics are summarized in **Table 4**.

Table 4: Demographics and Baseline Characteristics of Patients with Chronic GVHD

	REZUROCK 200 mg once daily (N=65)
Age, Median, Years (minimum, maximum)	53 (21, 77)
Age ≥ 65 Years, n (%)	17 (26)
Male, n (%)	42 (65)
Race, n (%)	
White	54 (83)
Black	6 (9)
Other or Not Reported	5 (8)
Median (range) time (months) from Chronic GVHD Diagnosis	25.3 (1.9, 162.4)
≥ 4 Organs Involved, n (%)	31 (48)
Median (range) Number of Prior Lines of Therapy	3 (2, 6)
Number of Prior Lines of Therapy, n (%)	
2	23 (35)
3	12 (19)
4	15 (23)
≥ 5	15 (23)
Prior chronic GVHD treatment with ibrutinib, n (%)	21 (32)
Prior chronic GVHD treatment with ruxolitinib, n (%)	20 (31)
Refractory to Last Therapy, n (%[a])	43/55 (78)
Severe chronic GVHD, n (%)	46 (71)

	REZUROCK 200 mg once daily (N=65)
Median (range) Global Severity Rating	7 (2, 9)
Median (range) Lee Symptom Scale Score at baseline	27 (7, 56)
Median (range) Corticosteroid dose at baseline (PE/kg)[b]	0.19 (0.03, 0.95)

[a] Denominator excludes patients with unknown status
[b] Prednisone equivalents/kilogram

The efficacy of REZUROCK was based on overall response rate (ORR) through Cycle 7 Day 1 where overall response included complete response or partial response according to the 2014 NIH Response Criteria. The ORR results are presented in **Table 5**. The ORR was 75% (95% CI: 63, 85). The median duration of response, calculated from first response to progression, death, or new systemic therapies for chronic GVHD, was 1.9 months (95% CI: 1.2, 2.9). The median time to first response was 1.8 months (95% CI: 1.0, 1.9). In patients who achieved response, no death or new systemic therapy initiation occurred in 62% (95% CI: 46, 74) of patients for at least 12 months since response.

Table 5: Overall Response Rate through Cycle 7 Day 1 for Patients with Chronic GVHD in Study KD025-213

	REZUROCK 200 mg once daily (N=65)
Overall Response Rate (ORR)	49 (75%)
95% Confidence Interval[a]	(63%, 85%)
Complete Response	4 (6%)
Partial Response	45 (69%)

[a] Estimated using Clopper-Pearson method

ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in the Lee Symptom Scale summary score through Cycle 7 Day 1 in 52% (95% CI: 40, 65) of patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

REZUROCK 200 mg tablets are supplied as pale yellow film-coated oblong tablets containing 200 mg of belumosudil (equivalent to 242.5 mg belumosudil mesylate). Each tablet is debossed with "KDM" on one side and "200" on the other side and is packaged as follows:

200 mg tablets in 30 count bottle: NDC 79802-200-30

Store at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Dispense to patient in original container only. Store in original container to protect from moisture. Replace cap securely each time after opening. Do not discard desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Embryo-fetal Toxicity*:*

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.1)*, *Use in Specific Populations (8.1, 8.3)]*.
- Advise females of reproductive potential to use effective contraceptive during treatment with REZUROCK and for at least one week after the last dose *[see Warnings and Precautions (5.1)]*.
- Advise males with female partners of reproductive potential to use effective contraceptive during treatment with REZUROCK and for at least one week after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with REZUROCK and for at least one week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

- Advise males and females of reproductive potential that REZUROCK may impair fertility *[see Use in Specific Populations (8.3)]*.

Administration

- Inform patients to take REZUROCK orally once daily with food according to their physician's instructions and that the oral dosage (tablets) should be swallowed whole with a glass of water without cutting, crushing or chewing the tablets approximately the same time each day *[see Dosage and Administration (2.1)]*.
- Advise patients that in the event of a missed daily dose of REZUROCK, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose *[see Dosage and Administration (2.1)]*.

Drug Interactions

- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*.

Active ingredient made in India.

Distributed and marketed by:

Kadmon Pharmaceuticals, LLC
Warrendale, PA 15086
1-877-377-7862

PATIENT INFORMATION
REZUROCK (REZ-ur-ok)
(belumosudil)
tablets

What is REZUROCK?

REZUROCK is a prescription medicine used to treat adults and children 12 years of age and older with chronic graft-versus-host disease (chronic GVHD) after you have received at least 2 prior treatments (systemic therapy) and they did not work.

It is not known if REZUROCK is safe and effective in children less than 12 years old.

Before taking REZUROCK, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney or liver problems.
- are pregnant or plan to become pregnant. REZUROCK can harm your unborn baby. If you are able to become pregnant, your healthcare provider will do a pregnancy test before starting treatment with REZUROCK. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with REZUROCK.
  - **Females** who can become pregnant should use effective birth control during treatment with REZUROCK and for at least 1 week after the last dose.
  - **Males** with female partners who can become pregnant should use effective birth control during treatment with REZUROCK and for at least 1 week after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if REZUROCK passes into breast milk. Do not breastfeed during treatment with REZUROCK and for at least 1 week after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. REZUROCK may affect the way other medicines work, and other medicines may affect the way REZUROCK works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take REZUROCK?

- Take REZUROCK exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking REZUROCK without first talking to your healthcare provider.
- Take REZUROCK 1 time a day with a meal.
- Take REZUROCK at about the same time each day.
- Swallow REZUROCK tablets whole with a glass of water.
- Do not cut, crush, or chew REZUROCK tablets.
- Your healthcare provider will do blood tests to check your liver at least 1 time a month during treatment with REZUROCK.
- If you miss a dose of REZUROCK, take it as soon as you remember on the same day. Take your next dose of REZUROCK at your regular time on the next day. Do not take extra doses of REZUROCK to make up for a missed dose.
- If you take too much REZUROCK, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of REZUROCK?

The most common side effects of REZUROCK include:

- infections
- tiredness or weakness
- nausea
- diarrhea
- shortness of breath
- cough
- swelling
- bleeding
- stomach (abdominal) pain
- muscle or bone pain
- headache
- high blood pressure

Your healthcare provider may change your dose of REZUROCK, temporarily stop, or permanently stop treatment with REZUROCK if you have certain side effects.

REZUROCK may affect fertility in males and females. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of REZUROCK.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Kadmon Pharmaceuticals, LLC at 1-877-377-7862.

How should I store REZUROCK?

- Store REZUROCK at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep REZUROCK in its original container. The REZUROCK bottle contains a desiccant packet to help keep your tablets dry (protect from moisture). Keep the desiccant in the bottle.

- Tightly close the REZUROCK bottle after you take your dose.

Keep REZUROCK and all medicines out of the reach of children.

General information about the safe and effective use of REZUROCK.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use REZUROCK for a condition for which it was not prescribed. Do not give REZUROCK to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about REZUROCK that is written for health professionals.

What are the ingredients in REZUROCK?

Active ingredient: belumosudil mesylate

Inactive ingredients:

Tablet core: microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

Tablet coating: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and yellow iron oxide.

Distributed and marketed by **Kadmon Pharmaceuticals, LLC**, Warrendale, PA 15086

For more information, call 1-877-377-7862 or go to www.REZUROCK.com.

This Patient Information has been approved by the U.S. Food and Drug Administration Issued: July 2021