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ADISINSIGHT REPORT

Belumosudil: First Approval

Hannah A. Blair[1]

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Abstract
Belumosudil (REZUROCK™) is a Rho-associated coiled-coil-containing protein kinase (ROCK) inhibitor that has been developed by Kadmon Pharmaceuticals for the treatment of chronic graft-versus-host disease (cGVHD) and systemic sclerosis. In July 2021, belumosudil received its first approval in the USA for the treatment of adult and paediatric patients aged ≥ 12 years with cGVHD after failure of at least two prior lines of systemic therapy. Belumosudil is under regulatory review in Australia, Canada, the UK and Switzerland for cGVHD. Clinical development for systemic sclerosis is ongoing in the USA. This article summarizes the milestones in the development of belumosudil leading to this first approval for the treatment of cGVHD.

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Belumosudil (REZUROCK™): Key Points

ROCK inhibitor being developed by Kadmon Pharmaceuticals for the treatment of cGVHD and systemic sclerosis

Received its first approval on 16 July 2021 in the USA

Approved for the treatment of adult and paediatric patients aged ≥ 12 years with cGVHD after failure of at least two prior lines of systemic therapy

1 Introduction

Belumosudil (REZUROCK™) is an orally active rho-associated coiled-coil-containing protein kinase (ROCK) inhibitor developed by Kadmon Pharmaceuticals for the treatment of chronic graft-versus-host disease (cGVHD) and systemic sclerosis. Under its Real-Time Oncology Review pilot program, the US FDA granted belumosudil orphan drug [1] and breakthrough therapy [2] designations for the treatment of cGVHD. In November 2020, the US FDA accepted the New Drug Application and granted a priority review [3]. On 16 July 2021, 6 weeks ahead of the PDUFA goal date, belumosudil received its first approval in the USA for the treatment of adult and paediatric patients aged ≥ 12 years with cGVHD after failure of at least two prior lines of systemic therapy [4, 5]. The recommended dosage of belumosudil is 200 mg once daily (with food) until progression of cGVHD that requires new systemic therapy [4]. The dosage of belumosudil should be increased to 200 mg twice daily in patients receiving concomitant strong CYP3A4 inducers or proton pump inhibitors [4].

Belumosudil is under regulatory review in Australia, Canada, the UK and Switzerland for cGVHD, and is in phase II development for cGVHD in China. Phase II development is ongoing in the USA for the treatment of systemic sclerosis. Development of belumosudil for the treatment of idiopathic pulmonary fibrosis, plaque psoriasis, non-alcoholic steatohepatitis, rheumatoid arthritis and systemic lupus erythematosus has been discontinued.

1.1 Company Agreements

In April 2011, Kadmon Pharmaceuticals entered into an agreement with Nano Terra under which Kadmon

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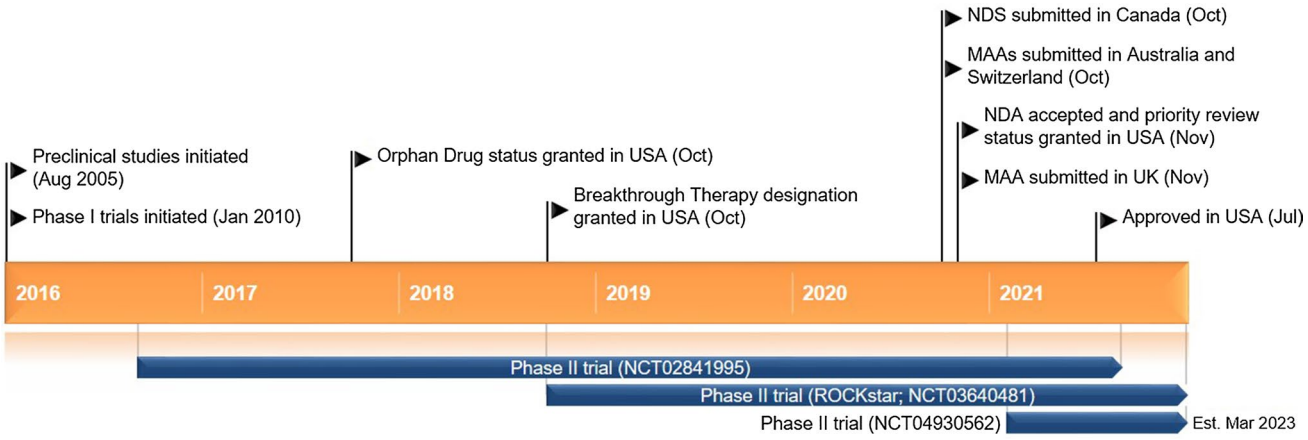
✉ Hannah A. Blair
dru@adis.com

[1] Springer Nature, Mairangi Bay, Private Bag 65901, Auckland 0754, New Zealand



Key milestones in the development of belumosudil, focusing on its use in the treatment of chronic graft-versus-host disease. *MAA* Marketing Authorisation Application, *NDA* New Drug Application, *NDS* New Drug Submission

Pharmaceuticals was granted a perpetual, worldwide exclusive license to three of Nano Terra's novel product candidates (including belumosudil), as well as rights to its drug discovery platform Pharmacomer™ Technology [6]. In November 2019, Kadmon Holdings and BioNova Pharmaceuticals formed a joint venture, BK Pharmaceuticals, to help accelerate the development and regulatory approval of belumosudil in China [7]. In December 2019, Kadmon Holdings and Meiji Seika Pharma formed a joint venture, Romeck Pharma, to exclusively develop and commercialise belumosudil in Japan and some other Asian countries [8].

1.2 Patent Information

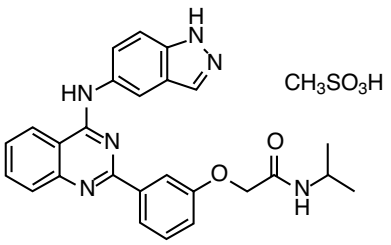
As of December 2020, belumosudil is covered under a US patent with market exclusivity in the USA and Japan until 2033. Kadmon Pharmaceuticals also has composition of matter and method of use patent protection for belumosudil with market exclusivity in the USA, Canada, China, Japan and Eurasia until 2026–2029. The company also has pending patent applications for belumosudil in the USA, Canada, China, Japan, Eurasia and Europe covering method of use with market exclusivity until 2033–2035.

2 Scientific Summary

2.1 Pharmacodynamics

Belumosudil is a ROCK inhibitor with half-maximal inhibitory concentrations (IC_{50}s) of ≈100 nM and 3 μM for ROCK2 and ROCK1, respectively [4]. Belumosudil downregulates proinflammatory responses by inhibiting signal transducer and activator of transcription 3 (STAT3) phosphorylation, upregulating STAT5 phosphorylation and shifting T helper 17 (Th17)/T regulatory (Treg) balance towards the Treg phenotype [9, 10].

Belumosudil effectively ameliorated cGVHD in multiple murine models [9]. In vitro, belumosudil inhibited aberrant pro-fibrotic signalling [4] via downregulation of pro-fibrotic gene transcription, stress fibre formation, myofibroblast activation and collagen deposition [11]. In human



Chemical structure of belumosudil

fibrosis-derived smooth muscle cells, belumosudil reduced connective tissue growth factor mRNA and remodelled the actin cytoskeleton [12]. In the lung endothelium, belumosudil promoted oxidative phosphorylation, inhibited glycolysis, intracellular pH and migration, and strengthened barrier integrity [13].

2.2 Pharmacokinetics

Approximately dose-proportional increases in belumosudil maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) are seen over a dosage range of 200–400 mg once daily [4]. The accumulation ratio of belumosudil is 1.4. Following once- or twice-daily administration of belumosudil 200 mg in patients with cGVHD, the median time to C_{max} at steady state was 1.26–2.53 h. When a single dose of belumosudil was administered with a high-fat and high-calorie meal, belumosudil C_{max} and AUC decreased 2.2-fold and 2-fold, respectively, while the median time to C_{max} was extended by 0.5 h. Following a single dose, belumosudil has a mean bioavailability of 64% [4].

The geometric mean volume of distribution of belumosudil is 184 L following a single dose [4]. The drug is 99.9% bound to human serum albumin and 98.6% bound to human α_1-acid glycoprotein. Belumosudil metabolism is mediated primarily by CYP3A4 and, to a lesser extent, by CYP2C8, CYP2D6 and UGT1A9. Following a single oral dose of radiolabeled belumosudil, 85% of the radioactivity is excreted in the faeces (30% as unchanged drug) and < 5% is excreted in the urine. In patients with cGVHD, the mean elimination half-life of belumosudil is 19 h and the clearance is 9.83 L/h. Age (18–77 years), sex, bodyweight (38.6–143 kg) and mild to moderate renal impairment [estimated glomerular filtration rate (eGFR) ≥ 60 and < 90 mL/min/1.73 m^2 to eGFR ≥ 30 and < 60 mL/min/1.73 m^2] had no clinically meaningful effect on the pharmacokinetics of belumosudil [4].

Belumosudil is an inhibitor of CYP1A2, CYP2C19, CYP2D6, UGT1A1 and UGT1A9, and also inhibits P-glycoprotein, BCRP and OATP1B1 at clinically relevant concentrations [4]. Belumosudil is a substrate of P-glycoprotein. Coadministration of belumosudil with strong CYP3A inducers (e.g. rifampin) or proton pump inhibitors (e.g. rabeprazole, omeprazole) decreases the C_{max} and AUC of belumosudil, which may reduce its efficacy. Coadministration of belumosudil with midazolam (a CYP3A substrate) is predicted to increase the C_{max} and AUC of midazolam ≈ 1.3- and 1.5-fold, respectively [4].

Features and properties of belumosudil

Alternative names	Belumosudil mesylate; KD-025; KD025 mesylate; BN-101; SLX-2119; REZUROCK™
Class	Acetamides; amines; anti-inflammatories; antifibrotics; antipsoriatics; antirheumatics; hepatoprotectants; indazoles; phenyl ethers; quinazolines; skin disorder therapies; small molecules
Mechanism of action	ROCK inhibitor
Route of administration	Oral
Pharmacodynamics	Downregulates proinflammatory responses by inhibiting STAT3 phosphorylation, upregulating STAT5 phosphorylation and shifting Th17/Treg balance towards Treg phenotype
Pharmacokinetics	Median time to C_{max} at steady state 1.26–2.53 h; mean bioavailability 64%; geometric mean volume of distribution 184 L; mean elimination half-life 19 h; clearance 9.83 L/h
Most frequent AEs	Infections, asthenia, nausea, diarrhoea, dyspnoea, cough, oedema, haemorrhage, abdominal pain, musculoskeletal pain, headache, ↓ phosphate, ↑ GGT, ↓ lymphocytes, hypertension
ATC codes	
WHO ATC code	L04A-A48 (belumosudil)
EphMRA ATC code	L4 (immunosuppressants)
Chemical name	2-[3-[4-(1H-indazol-5-ylamino)quinazolin-2-yl]phenoxy]-*N*-propan-2-ylacetamide

↓ decreased, ↑ increased, *AEs* adverse events, C_{max} maximum plasma concentration, *GGT* γ-glutamyl transferase, *ROCK* rho-associated coiled-coil-containing protein kinase, *STAT* signal transducer and activator of transcription, *Th17* T helper 17 cells, *Treg* regulatory T cells

2.3 Therapeutic Trials

2.3.1 Chronic Graft-Versus-Host Disease

The efficacy of belumosudil for the treatment of cGVHD was demonstrated in the randomized, multicentre, phase II ROCKstar trial in allogeneic haematopoietic cell transplant (alloHCT) recipients (NCT03640481) [14]. After a median follow-up of 14 months, the best overall response rate (ORR, defined as complete response or partial response; primary endpoint) was 74% (95% CI 62–84%) with belumosudil 200 mg once daily and 77% (95% CI 65–87%) with belumosudil 200 mg twice daily. Responses were observed in all affected organ systems and across all patient subgroups. The ORR was 74% in patients who previously received ibrutinib ($n = 46$) and 68% in patients who previously received ruxolitinib ($n = 38$). In this study, 132 patients aged ≥ 12 years with persistent cGVHD manifestations after receiving 2–5 prior systemic lines of therapy were randomized to receive oral belumosudil 200 mg once or twice daily until clinically significant progression of cGVHD or unacceptable toxicity. Randomization was stratified by cGVHD severity and prior exposure to ibrutinib. At baseline, 99% of patients were receiving concomitant corticosteroids. The median time to response was 5 weeks, with most (91%) responses seen within the first 6 months of treatment. Responses were maintained for ≥ 20 weeks in 59% of patients. The median duration of response was 54 weeks. Clinically meaningful improvement (≥ 7-point reduction) from baseline in the Lee Symptom Scale (LSS) score was observed in 59% of patients receiving belumosudil 200 mg once daily and 62% of patients receiving belumosudil 200 mg twice daily; LSS improvements were seen in both responders and non-responders. Corticosteroid doses were reduced in 65% of patients. The overall failure-free survival (FFS) rate was 75% at 6 months and 56% at 12 months. The overall survival (OS) rate at 2 years was 89% [14].

In an earlier open-label, multicentre, phase II, dose-finding trial in allogeneic bone marrow transplant or alloHCT recipients (NCT02841995), belumosudil was an effective treatment for cGVHD [15]. After a median follow-up of 29 months, 65% (95% CI 51–77%) had an ORR (primary endpoint). Responses were seen in all affected organs and across all patient subgroups, including patients who had received ≥ 2 prior systemic lines of therapy and patients with ≥ 4 organs involved. The study enrolled 54 patients aged ≥ 18 years with persistent cGVHD manifestations after 1–3 prior systemic lines of therapy and who were receiving corticosteroids with or without a calcineurin inhibitor and/or concurrent extracorporeal photopheresis. Patients in three sequential cohorts received oral belumosudil 200 mg once daily, 200 mg twice daily or 400 mg once daily in 28-day cycles until cGHVD progression or unacceptable toxicity. Most (> 75%) responses were achieved during the first 8 weeks of treatment and the median duration of response was 35 weeks. Fifty percent of patients reported a clinically meaningful improvement in LSS score and 67% of patients were able to reduce their corticosteroid dose. The median time to next treatment was 14 months. FFS rates at 6, 12 and 24 months were 76, 47 and 33%, respectively, and the 2-year OS rate was 82% [15].

Key clinical trials of belumosudil

Drug	Indication	Phase	Status	Location	Sponsor	Identifier
Belumosudil	cGVHD	II	Recruiting	USA	Kadmon Corporation	ROCKstar; NCT03640481
Belumosudil	cGVHD	II	Active, no longer recruiting	USA	Kadmon Corporation	NCT02841995
Belumosudil	cGVHD	II	Recruiting	China	BioNova Pharmaceuticals	NCT04930562
Belumosudil	Systemic sclerosis	II	Recruiting	USA	Kadmon Corporation	NCT04680975
Belumosudil	Systemic sclerosis	II	Recruiting	USA	Kadmon Corporation	NCT03919799

cGVHD chronic graft-versus-host disease

2.4 Adverse Events

Belumosudil was well tolerated when used to treat cGVHD in phase II trials [14, 15]. In a pooled analysis of both trials, the most common (incidence ≥ 20%) AEs with belumosudil 200 mg once daily ($n = 83$) were infection (53%), asthenia (46%), nausea (42%), diarrhoea (35%), dyspnoea (33%), cough (30%), oedema (27%), haemorrhage (23%), musculoskeletal pain (22%), abdominal pain (22%), headache (21%) and hypertension (21%) [4]. The most common (incidence ≥ 5%) grade 3–4 AEs, including laboratory abnormalities, were infection (16%), decreased lymphocytes (13%), increased γ-glutamyl transferase (11%), hypertension (7%), decreased phosphate (7%), decreased platelets (5%), diarrhoea (5%), dyspnoea (5%) and haemorrhage (5%). AEs leading to discontinuation of belumosudil occurred in 18% of patients while AEs leading to dose interruption occurred in 29% of patients. One patient experienced a fatal AE (severe nausea, vomiting, diarrhoea and multi-organ failure) [4].

Based on animal studies and its mechanism of action, belumosudil may cause foetal harm when administered to pregnant women, who should be advised of the potential risk [4]. Breastfeeding is not recommended during treatment with belumosudil and for ≥ 1 week after the last dose due to the potential for belumosudil to be excreted in milk, which could lead to serious adverse reactions [4].

2.5 Ongoing Clinical Trials

In addition to the ongoing phase II cGVHD trials described above (NCT03640481 and NCT02841995), an open-label, multicentre, phase II trial (NCT04930562) is currently recruiting patients in China. The trial plans to evaluate the efficacy and safety of belumosudil 200 mg once daily in patients with cGVHD after at least first line of systemic therapy.

Patients with diffuse cutaneous systemic sclerosis are being recruited in two phase II trials: an open-label, multicentre trial evaluating the efficacy and safety of belumosudil 200 mg twice daily (NCT04680975) and a randomized, double-blind, placebo-controlled trial with an open-label extension evaluating the efficacy and safety of belumosudil 200 mg once or twice daily (NCT03919799).

3 Current Status

Belumosudil received its first approval in the USA on 16 July 2021 for the treatment of adult and paediatric patients aged ≥ 12 years with cGVHD after failure of at least two prior lines of systemic therapy [5].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-021-01593-z.

Declarations

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Authorship and Conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Hannah Blair is a salaried employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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