03 February 2026
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Rezurock (2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt)
Treatment of graft-versus-host disease
EU/3/19/2205

Sponsor: Sanofi Winthrop Industrie

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt
Other name(s)	Rezurock, Belumosudil
International Non-Proprietary Name	Belumosudil mesIlate
Tradename	Rezurock
Orphan condition	Treatment of graft-versus-host disease
Sponsor's details:	Sanofi Winthrop Industrie 82 Avenue Raspail 94250 Gentilly France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Quality Regulatory Clinical Ireland Limited
COMP opinion	12 September 2019
EC decision	17 October 2019
EC registration number	EU/3/19/2205
Post-designation procedural history	
Transfer of sponsorship	Transfer from Quality Regulatory Clinical Ireland Limited to Sanofi-Aventis Groupe – EC decision of 04 March 2022 Transfer from Sanofi-Aventis Groupe to Sanofi Winthrop Industrie – EC decision of 31 March 2023
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johanna Lähteenvuo / Beata Maria Jakline Ullrich
Applicant	Sanofi Winthrop Industrie
Application submission	19 September 2024
Procedure start	03 October 2024
Procedure number	EMA/H/C/006421/0000
Invented name	Rezurock
Proposed therapeutic indication	is indicated for the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy. Updated 10.01.2024: Treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy. Further information on Rezurock can be found in the European public assessment report (EPAR) on the Agency's website : https://www.ema.europa.eu/en/medicines/human/EPAR/Rezurock

CHMP opinion	29 January 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
Sponsor's report submission	15 April 2025
COMP discussion	20-22 January 2026
COMP opinion (adoption via written procedure)	03 February 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2019 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt was considered justified based on preliminary clinical data in patients with chronic graft-versus-host disease showing a significant improvement in a validated primary endpoint of overall response rate;
- the condition is chronically debilitating and life-threatening in particular due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections;
- the condition was estimated to be affecting approximately 0.8 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate responses in previously treated patients as well as a reduction in corticosteroid use. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt as an orphan medicinal product for the orphan condition: treatment of graft-versus-host disease.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Graft versus host disease (GVHD) is a pleiotropic multiorgan syndrome occurring in up to 60% of patients after haematopoietic stem cell transplantation (HCT) from an allogeneic donor (Lee, 2017). GVHD is the major non-relapse complication associated with allogeneic HCT (Piper & Drobyski, 2019) and is defined as a reaction of donor immune cells against host tissues. There are two types of GVHD referred to as acute and chronic. Acute GVHD (aGVHD) tends to occur in the first 100 days after a transplant, although it can begin later and affects the skin, stomach, intestines and liver (Jacobsohn & Vogelsang, 2007). Chronic GVHD (cGVHD) typically begins more than 100 days after transplant and affects the skin, eyes, mouth, gut, liver, lungs, joints, and genitourinary system (Horwitz & Sullivan, 2006). The current consensus is that clinical manifestations, and not the time to symptomatic onset after transplantation, determine whether the clinical syndrome of GVHD is considered acute or chronic (Filipovich, et al., 2005) (Jagasia, et al., 2015).

Chronic GVHD remains the major cause of late non-relapse death following HCT. The onset of cGVHD may follow directly from aGVHD or may overlap with aGVHD. A major risk factor for cGVHD is the onset of aGVHD. Immune cells and organs e.g., thymus and spleen are the primary target organs of aGVHD. Thymus destruction and deficient selection of donor T cells by the thymus are the major factors resulting in allo- and autoimmunity associated with cGVHD. A hallmark of cGVHD is the identification of sclerotic lesions which can occur in almost every organ of the body. Recently a role for Th17 cells in the development of sclerosis has been reported (Ghimire, et al., 2017).

The approved therapeutic indication "REZUROCK is indicated for the treatment of adults and paediatric patients (12 years and older with a body weight of at least 40 kg) with **chronic graft-versus-host disease (cGVHD)** when **other treatment options** provide **limited clinical benefit**, are **not suitable**, **or have been exhausted**" falls within the scope of the designated orphan condition "Treatment of graft-versus-host disease".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

At the time of the initial designation the COMP agreed that the condition was chronically debilitating and life-threatening. This view is maintained by the committee.

Graft-versus-host disease usually affects multiple organs—most commonly the skin, liver, gastrointestinal tract, lungs, and eyes—and can lead to progressive, long-term organ damage. Chronic GvHD often causes persistent inflammation, scarring, and loss of organ function.

Patients can develop debilitating symptoms, such as chronic pain, severe dry eyes and mouth, malabsorption, muscle weakness, skin tightening, and impaired mobility. Over time, these complications can significantly reduce independence and quality of life.

GvHD is also life-threatening, as it increases susceptibility to serious infections (due to both the disease and the immunosuppressive treatments required), can lead to respiratory failure, liver dysfunction, or severe gastrointestinal complications, and is associated with high long-term mortality.

In conclusion, GvHD is chronically debilitating due to multi-organ damage and long-term disability, and it is life-threatening due to high infection risk and organ failure.

Number of people affected or at risk

The sponsor proposes a complete prevalence estimate for cGVHD of 0.69 in 10,000 persons.

This estimate is based on data from the European Society for Blood and Marrow Transplantation (EBMT), as the majority of studies identified by the sponsor as sources of relevant data for incidence of cGVHD have been retrospective studies conducted using data from the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centres, mainly in Europe.

The EBMT regularly reports data on the number of transplants conducted by the transplant centres, with the latest report published in 2024 based on an activity survey from 2022 (Passweg, et al., 2024). This 2022 activity survey of the EBMT reported a total of 46,143 haematopoietic cell transplants (HCT) conducted in 50 European and affiliated countries (Passweg, et al., 2024), of which 19,011 transplants were allogeneic. The EBMT activity survey has been conducted annually since 1990 (Passweg, et al., 2018), with a continuing trend of increase in the numbers of patients transplanted reported.

Chronic GVHD requires long-term immunosuppressive therapy after HCT, often for more than 2 years. The median duration of treatment reported in the literature varies from 0.75 to 5.75 yrs (see Table 1).

Table 1. Median duration of treatment for chronic GVHD

Reference	**Median Duration**	**N**
(Stewart, et al., 2004)4	0.96 yrs	751
(Lee, Vogelsang, & Flowers, 2003)	0.75 yrs	82
(Arora, et al., 2011)	2-3 yrs	5343
(Lee, et al., 2018)	5.75 yrs	250
(Martin, Inamoto, Carpenter, Lee, & Flowers, 2011)	2 yrs in patients with HCT with marrow cells 3.5 yrs in pts with HCT with growth factor mobilised cells	71
(Zeiser, et al., 2023)	0.46 yrs	164
(Zeiser, et al., 2023)	1.01 yrs	165
Estimated duration (mean)	[(0.96* 751) + (0.75*82) + (2.5*5343) + (5.75*250) + (2.75*71)] / 6497 = 2.3 yrs	

Using the data presented above, a conservative approach has been taken in calculating the prevalence of cGVHD in Europe. Based on the number of Haematopoietic Stem Cell Transplantations reported in the 2022 EBMT survey and assuming a worst-case scenario of 70% patients developing cGVHD, it is estimated that 13,308 patients will have developed cGVHD in 2022. The Eurostat population estimate

for European Union in 2022 was 446,735,300, equating to an incidence of 0.30 in 10,000. Assuming a median duration of 2.4 years, the complete prevalence is thus calculated to be 0.69 in 10,000.

While the COMP accepts the EBMT as a valid data source, the restriction to the patient subset of cGvHD is not supported in view of the broader orphan condition of GvHD. Considering this, the COMP preferred to maintain their previously accepted prevalence estimate for the overarching condition of GvHD of approximately 1 in 10,000 persons.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Corticosteroids, with or without calcineurin inhibitors (CNIs) remain the standard first-line treatment for cGVHD requiring systemic therapy. Jakavi (ruxolitinib) is the only approved therapy available in the EU for the treatment of cGVHD in second line of treatment and above.

Table 2. Summary of currently approved pharmacotherapies for the treatment of GvHD/cGvHD in Europe

Active Substance	Authorization	Authorized Indication (GvHD related)
Methylprednisolone (Numerous generic products)	National and MR authorisations (e.g. France)	Treatment of graft-versus-host-disease
Prednisolone (Numerous generic products)	National and MR authorisations (e.g. France)	Treatment of graft-versus-host-disease
Prednisone (Numerous generic products)	National and MR authorisations (e.g. France)	Treatment of graft-versus-host-disease
Ciclosporin (Sandimmun, Neoral as well as numerous generic products)	Various national and MR authorisations	Treatment of graft-versus-host-disease
Ruxolitinib (Jakavi)	Centralised Authorisation	Jakavi is indicated for the treatment of adults and paediatric patients aged 6 months and older with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

For the treatment of GvHD after stem-cell transplantation for haematological malignancies, consensus recommendations were published by the European Society for Blood and Marrow Transplantation (EBMT) in 2020 (Penack et al., 2020) and updated in 2022 (Penack et al., 2024). Of note, in the updated EBMT recommendations, belumosudil (authorized by FDA in 2021) is listed as a possible treatment option for adults with steroid-refractory chronic graft-versus-host disease (SR-cGVHD), after

ruxolitinib failure or ruxolitinib intolerance and contraindications, if inclusion into a clinical trial is not possible.

Of note, it has been reported that more than 47% of patients progress to 3 or more lines of therapy (LOT) primarily due to lack of efficacy and/or toxicity leading to discontinuation with potential for disease progression (Flowers & Martin, 2015) (Bachier, et al., 2021). Long-term, approximately one-third of patients with cGVHD have relapsed or died, a third have discontinued therapy successfully and a third remain on long-term treatment for cGVHD. Of patients who remain on therapy long-term, half progress to fourth- or fifth-line therapy (Lee, et al., 2018).

Whilst Jakavi® (ruxolitinib) is now authorized for the treatment of patients with cGVHD who have inadequate response to steroids, the sponsor notes that there is still no authorized treatment for patients who are non-responsive to multiple prior lines of therapy, including ruxolitinib.

For the purpose of this procedure, all products listed above in table 2 are considered satisfactory methods.

Significant benefit

The sponsor proposes that Rezurock represents a clinically relevant advantage over currently authorized pharmacotherapies (i.e. improved efficacy and improved safety), as well as a major contribution to patient care (once daily oral dosing, less need for dose adjustments and safety monitoring due to adverse effects on platelets and other hematologic parameters, such as required for ruxolitinib).

Clinically relevant advantage based on efficacy in patients whose symptoms could not be controlled with currently authorized therapies:

In the treatment sequencing paradigm, belumosudil has been positioned after ruxolitinib, and as such represents a therapeutic option for patients who have received at least 2 prior lines of systemic therapy, for which there are no therapies currently authorised.

The clinical benefit in patients with cGvHD whose symptoms could not be controlled with currently authorized products has been established through study KD025-213, which was a phase 2, non-controlled, randomized, multicentre study to evaluate the efficacy and safety of belumosudil (KD025) in subjects with cGVHD after at least 2 prior lines of systemic therapy. Eligible subjects were randomized to open-label treatment arms belumosudil 200 mg QD (arm A) or belumosudil 200 mg BID (arm B). The study did not include a reference study arm. The requested posology is 200 mg QD, therefore results of Arm A are of particular interest and are described below. Arm A included 77 adults and 2 adolescents. All subjects received a previous allogeneic haematopoietic stem cell transplantation.

The majority (73%) of patients had severe cGVHD disease. The median number of prior lines of systemic cGVHD therapy was three. Most frequently prior used systemic treatments were corticosteroids (99%) and calcineurin inhibitors (64%); around 38% of patients had received prior ruxolitinib treatments. The majority of patients were refractory to their last systemic therapy prior to study enrolment. Fifty-one percent of patients had four or more organs involved. All subjects were taking a concomitant cGVHD medication. The most frequently used systemic concomitant treatments that the patients taking on Cycle 1 Day 1 in the study were corticosteroids (99%) and calcineurin inhibitors (tacrolimus or cyclosporin, 40%). The study also enrolled 2 adolescent patients, ages 12 and 13 years, to the 200 mg once daily arm. The primary endpoint was overall response rate (ORR) at any time while on treatment (defined by the 2014 NIH Consensus Response Criteria).

The ORR observed in the 77 patients (modified ITT population) receiving the 200 mg QD dose of belumosudil was 74%. There were no significant differences in ORR between clinically relevant subgroups, including in patients receiving prior treatment with ruxolitinib (see Figure 1). The ORR in the 200 mg QD dose group was also consistent with the one observed in the 200 mg BID dose group of belumosudil which was 76%, and in clinically relevant subgroups thereof (including in patients receiving prior treatment with ruxolitinib). The sponsor further emphasized that the ORR observed for belumosudil overall and at 200 mg QD were consistently higher than the predetermined target ORR of 30% regardless of subgroups, that were cGVHD severity (severe yes or no), number of prior lines of therapy (<4 or ≥4), prior ibrutinib (yes or no), prior ruxolitinib (yes or no), or best response to the last prior treatment (refractory or non-refractory).

Of note, in the final SmPC for belumosudil, following the re-examination procedure at the CHMP, the main efficacy data is reported in the ITT population (as compared to the above modified ITT population) consisting of 78 patients (instead of 77 patients). The ORR in this ITT population was 73.1 (95% CI 61.8, 82.5), comprised of a complete response rate of 5.1% and a partial response rate of 67.9%. The reported median duration of response was 23.9 weeks (95% CI 11.43, 50.43).

Figure 1. Forest plot for subgroup analyses of ORR (mITT population, 200mg QD cohort) – Belumosudil from KD025-213 Study

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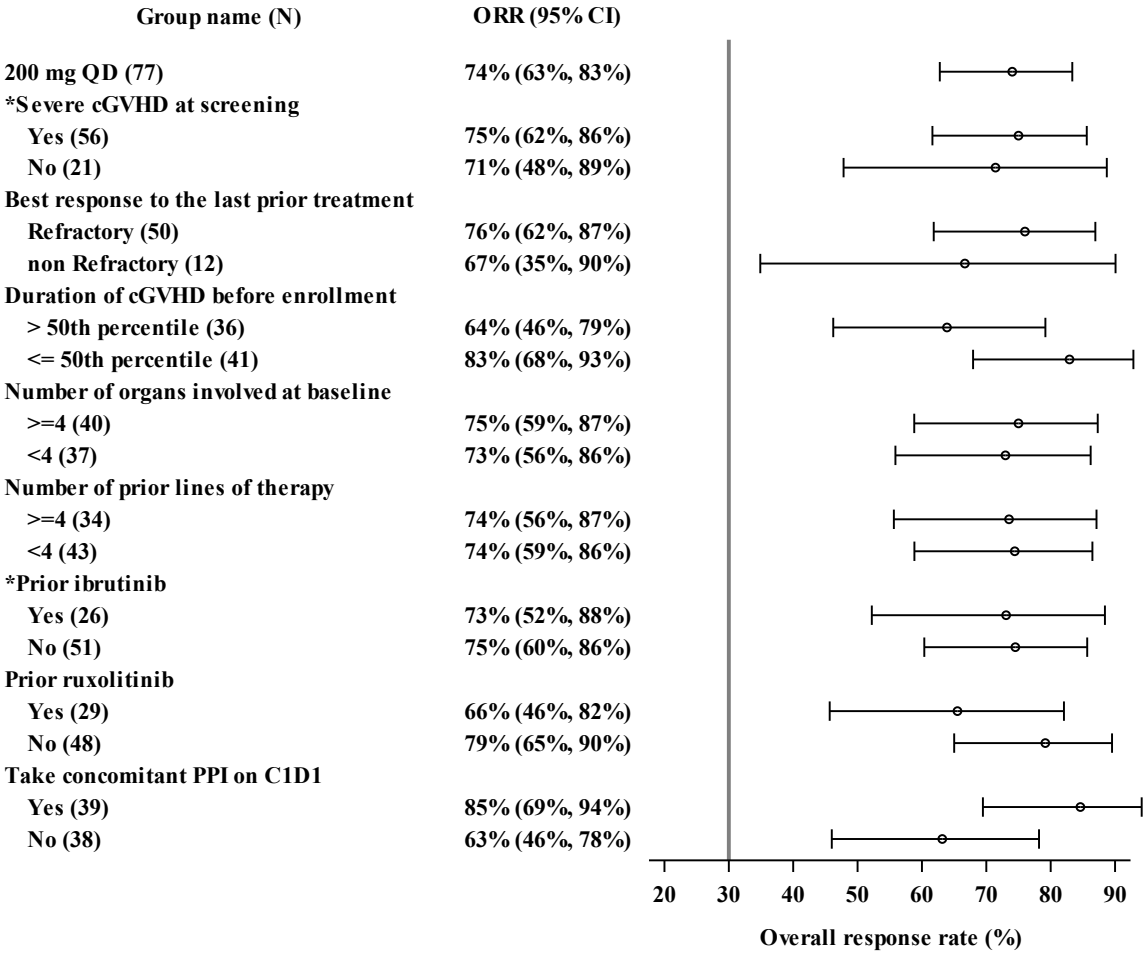
Figure 1.1.12
Forest plot of subgroup analysis of overall response rate (ORR) for 200 mg QD arm (mITT population)



Note:
- *: Indicates stratification factors.
- ORR = Overall response rate; CI = confidence interval, CI is calculated using Clopper–Pearson interval (exact) method.
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.

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The COMP considered that the efficacy data, as described above, establishes the significant benefit of Rezurock over currently authorized medicinal products. The sponsor has provided clinical data showing that Rezurock achieved responses which were considered clinically relevant in heavily pretreated patients with chronic graft versus host disease whose disease symptoms could not be sufficiently

controlled with currently authorized medicinal products, including ruxolitinib. The Committee considered that this constitutes a clinically relevant advantage.

The sponsor also presented a significant benefit claim of belumosudil based on major contribution to patient care (ease of administration and reduced monitoring requirements) over ruxolitinib. However, the COMP considered that these claims have not been sufficiently substantiated.

In addition, the sponsor presented a significant benefit claim of belumosudil based on improved safety over ruxolitinib. However, the COMP considered that these claims could not be sufficiently supported with available data.

In conclusion, the COMP adopted a positive opinion on orphan maintenance, accepting that GvHD remains a rare condition with a prevalence estimate of approximately 1 in 10,000 and Rezurock representing a significant benefit due to its intended clinical use in cGvHD patients, whose disease symptoms could not be sufficiently controlled with currently authorized medicinal products, including ruxolitinib.

4. COMP position adopted on 03 February 2026

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of graft-versus-host disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to impairment of essential organ function, high infection risk and metabolic complications;
- although satisfactory methods for the Treatment of the condition have been authorised in the European Union, the claim that Rezurock is of significant benefit to those affected by the orphan condition is established. The sponsor has provided clinical data showing that Rezurock achieved responses which were considered clinically relevant in heavily pretreated patients with chronic graft versus host disease whose disease symptoms could not be sufficiently controlled with currently authorized medicinal products, including ruxolitinib. The Committee considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Rezurock, 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt, belumosudil mesilate for treatment of graft-versus-host disease (EU/3/19/2205) is not removed from the Community Register of Orphan Medicinal Products.