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Full Length Article
Analysis

Transportability to the European Population of Efficacy of Belumosudil as Compared With Physician's Choice of Best Available Therapy for the Treatment of Chronic Graft Versus Host Disease

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Belumosudil was approved by US Food and Drug Administration in July 2021 for the treatment of relapsed/refractory chronic graft-versus-host disease (cGVHD) in patients aged ≥12 years after failure of at least 2 prior lines of therapy (LOTs). By comparing the treatment response pattern of patients between the Europe and US, this transportability analysis modelled belumosudil's effect in European patients based on the observed effect in real-world US patients. This ROCKreal study used a targeted maximum likelihood

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Belumosudil
Line of therapy
Overall response rate

estimation-based transportability analysis to compare treatment-response pattern in Europe and US to evaluate the potential efficacy of belumosudil compared with BAT for treatment of cGVHD in European patients after failure of 2 to 5 prior LOTs. This analysis generalized US ROCKreal study findings to European patients. Data was collected on 196 US and 222 European patients ≥12 years of age with cGVHD treated with 2 to 5 prior LOTs with visits between March 2015 and 2024 from 8 US and 32 European sites. Sustained steroid reduction is recognized as a clinically meaningful indicator of benefit in late-line cGVHD, consistent with prior work examining composite clinical benefit measures. The primary endpoint was the adjusted (causal) ratio in 6-month overall response rate (ORR), defined using a prespecified sequential algorithm incorporating NIH consensus criteria, physician assessment, and ≥50% corticosteroid taper without progression. Because outcomes were not collected for European patients, efficacy endpoints were transported using US outcome models. A supplementary endpoint, the adjusted (causal) difference in 6-month ORR, was also evaluated. At LOT initiation, median age (52.6 versus 57.6 years) and rate of severe cGVHD (40% versus 51%) were lower in Europe than the US; otherwise, populations were well-balanced. Efficacy was defined as ORR at 6 months post-LOT initiation when treated with belumosudil versus best available therapy (BAT). Using targeted maximum likelihood estimation, an outcome model was trained on US data. Treatment-specific responses were predicted using European patient characteristics, resulting in an estimated ORR of 37.6% when treated with belumosudil versus 26.3% with BAT (ORR ratio = 1.427 95% CI: [1.05, ∞); *P*-value: .03]). In line with positive efficacy results observed in previous real-world evidence studies in US and European patients, findings from this transportability analysis indicate that the treatment-response pattern are similar in Europe compared to US and cGVHD patients treated with belumosudil would have significantly more clinical benefit compared to BAT in Europe.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) remains a long-term complication of allogeneic hematopoietic stem cell transplantation (alloHSCT), often leading to reduced quality of life and higher morbidity and mortality [1–3]. Corticosteroids (CS) alone or in combination with calcineurin inhibitors (CNIs) are recommended for use as first-line treatments, however, more than 70% of patients require a subsequent line of therapy (LOT) [4,5]. Targeted agents, like ruxolitinib, have been approved for treating steroid-refractory cGVHD in the United States (US) and Europe, while others, like ibrutinib, have only been approved in the US [5–7]. However, many patients require an additional line of treatment due to disease progression or intolerance to current therapies [7,8].

Belumosudil is the first available inhibitor of rho-associated coiled-coil containing protein kinase (ROCK) 2. ROCK 2 inhibition downregulates T helper 17 (Th17) cells via signal transducer and activator of transcription 3 (STAT 3) and upregulates regulatory T (Treg) cells via signal transducer and activator of transcription 5 (STAT 5) pathways, respectively, thereby restoring immune homeostasis [9,10]. The US Food and Drug Administration (FDA) approved belumosudil in July 2021 for the treatment of cGVHD in patients ≥12 years old after failure of at least 2 prior LOTs based on the randomized phase II dose finding ROCKstar trial [11]. Although approval of some novel targeted agents are based on phase II single-arm studies [11,12], this does not provide context relative to other therapies. The ROCKreal study, a noninterventional study conducted across 8 academic sites in the US, evaluated the efficacy of belumosudil compared with clinician-chosen best available therapy (BAT) for treatment of cGVHD in patients after failure of 2 to 5 prior LOTs. Prespecified analyses comparing US patients treated with belumosudil or BAT with blinding of data until the point of outcome analysis demonstrated an increased 6-month overall response rate (ORR) on belumosudil compared with BAT [13].

Since belumosudil is not yet an approved treatment for cGVHD in Europe, transportability analysis can model the treatment effect observed in the US population to comparable European patients based on patient baseline characteristics from US and Europe. These data would provide timely evidence of its potential benefits. Transportability

analysis is used to transport causal effects from experimental studies to new populations where randomized trials aren't feasible [14,15]. Technical requirements under which an estimated effect can be transported from a source population to an external target population have been described [16]. The validity of a transportability analysis depends on 3 key assumptions: first, that treatment effects are consistent across populations when conditioned on measured covariates (conditional exchangeability); second, that the target population is adequately represented in the source population (positivity); and third, that patient outcomes are independent (stable unit treatment value). When these assumptions hold, the treatment effect in Europe can be accurately estimated using a targeted maximum likelihood estimation (TMLE)-based transportability analysis, which adjusts for baseline differences in the Europe target population and US source population [17]. TMLE is preferred over matching because it uses the entire study population and is more generalizable than matching, which relies only on the propensity score and ignores covariate-outcome relationships, TMLE models both the outcome regression and the propensity score, making it more efficient by leveraging more data [17] and is increasingly recognized as valid tool for real-world analyses of treatment outcomes [18]. This study used a TMLE-based transportability analysis to evaluate the effectiveness of belumosudil compared with BAT for treatment of cGVHD in European patients after failure of 2 to 5 prior LOTs.

METHODS

Real World Study Design

This transportability analysis generalized findings from the US ROCKreal study to European patients. Data from retrospective patient charts were collected from the 2 populations with a uniform selection criterion, precise definitions of the treatment and comparator of interest, and prespecified definition of the primary endpoint. Figure 1 summarizes the general study design. The study design was aligned with the EMA reflection paper on noninterventional studies [19].

DATA SOURCE

Patient data from transplant recipients identified as having cGVHD were extracted from medical charts and entered into an electronic data collection form by trained personnel at 8 transplant centers in the US and 32 sites from Europe (Table S1) under local IRB-approved protocols granting waiver of consent for accessing de-identified clinical data. Clinical experts constructed an extensive list of potential confounders, including demographic information, cGVHD treatment history, and transplant history in alignment with baseline information collected as part of the ROCKstar trial [11].

European chart abstraction included baseline demographic and clinical characteristics only; outcome data, including ORR and failure-free survival, were not collected. The CRF was designed with clinical experts from Emory University. Over 27 clinical characteristics were included both from European and US patients on transplant history, medication history, and cGVHD history.

Eligibility Criteria

Patients ≥12 years old with cGVHD who received 2 to 5 prior LOTs and had no prior belumosudil exposure were eligible to be included in the study. Patients receiving any of the following BAT in lines 3 to 6 were included: extracorporeal photopheresis, mycophenolate mofetil, rituximab, methotrexate, sirolimus, ruxolitinib, ibrutinib, imatinib, abatacept, alemtuzumab, etanercept, hydroxychloroquine, interleukin-2, pentostatin, tacrolimus, cyclosporine, CS and nodal irradiation. Patients with less than 1-year history of cGVHD treatment, prior cGVHD clinical trial participation, or documented relapse of underlying malignancy prior to LOT initiation were excluded.

In the US, baseline demographic, clinical, and treatment history data as well as outcomes data were collected from 8 cGVHD-specialized sites. In Europe, demographic, clinical, and treatment history data (but not outcomes) were gathered from 32 transplant centers across Great Britain, France, Italy, Germany, and Spain. The focus of data queries with sites was on ensuring completeness and accuracy of key measures, such as the start and end dates of systemic agents.

Line of Therapy (LOT)

A consistent definition of what comprised an LOT was applied across all sites (Figure S1). LOT initiation was defined as: (1) Treatment with a new systemic agent; (2) Reinitiation of a previous agent after other agents were used in the interim; (3) CS initiation, if it was the first use or the dose increased to ≥1 mg/kg/day. LOTs received <2 weeks and occurring after belumosudil were excluded. Further details on the algorithm used to define LOTs can be found in the initial US based ROCKreal publication [13].

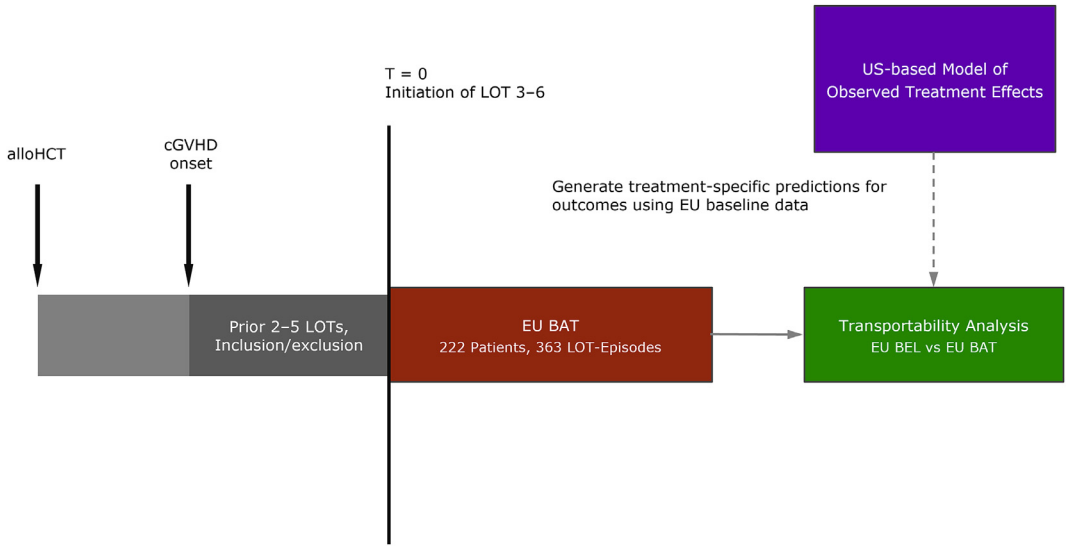

Figure 1. Study design of transportability analysis to estimate the effectiveness of belumosudil versus BAT in European population. The US-based model of observed treatment effects is described in the ROCKreal study [13].

Patients Contributing Multiple LOTs

Patients could be eligible for the study at multiple points (e.g., initiation of 3rd to 6th LOT) and contributed all eligible treatment episodes. This allowed the ROCKreal study to assess the effectiveness of belumosudil versus BAT in the US. Transporting the effect estimate to European patients required capturing baseline data on those contributing eligible LOTs 3 to 6.

Efficacy Endpoint

The primary objective in the ROCKreal study was to evaluate the efficacy, defined as the 6-month ORR of belumosudil versus BAT in patients with cGVHD that have failed to respond, or maintain response, to 2 to 5 prior LOTs. Further details on the composite definition of 6-month ORR defined as the proportion of complete or partial responses based on 2014 NIH consensus criteria, physician assessment, or (CS) dose taper of $\geq$50% without cGVHD progression can be found in the ROCKreal US study [13]. Sustained steroid reduction is recognized as a clinically meaningful indicator of benefit in late-line cGVHD, consistent with prior work examining composite clinical benefit measures [20]. The composite 6 months ORR was assigned using a prespecified sequential algorithm. Documented NIH-defined CR/PR or physician-assessed response/progression, death, relapse, or initiation of a new LOT were evaluated first. A $\geq$50% corticosteroid taper without progression was applied only when no definitive response information was available and the patient remained clinically stable, ensuring conservative classification. The primary endpoint was defined as the adjusted (causal) ratio in ORR at 6 months, and a supplementary efficacy endpoint, the adjusted (causal) difference in ORR at 6 months, was also evaluated.

In the US, baseline demographic, clinical, and treatment history data as well as outcomes data were collected from 8 cGVHD-specialized sites. In Europe, demographic, clinical, and treatment history data (but not outcomes) were gathered from 32 transplant centers across Great Britain, France, Italy, Germany, and Spain. Because outcomes were not collected for European patients, efficacy endpoints were transported using US outcome models. The focus was on ensuring completeness and accuracy of key measures, such as the start and end dates of systemic agents.

Statistical Analysis

Descriptive statistics and comparisons between populations

Baseline characteristics at Europe and US LOT initiation were assessed via unadjusted descriptive analysis. Potential confounders, including demographic information, cGVHD treatment history, transplant history, and specific treatment-related variables (e.g., history of ruxolitinib use, number of prior LOTs) were summarized and compared between the US and Europe. Missing baseline covariate values (Table S2) were imputed as the mean for continuous covariates and the mode for binary covariates. Imputation indicators were included as adjustment variables to address any informative patterns.

Primary transportability analysis

The ROCKreal US study employed target trial emulation and TMLE (an advanced causal inference methodology) to adjust for nonrandomization and right informative censoring, to evaluate the 6-month adjusted ORR when treated with belumosudil or BAT as well as the ORR ratio and ORR difference of belumosudil versus BAT in the US [13,21]. TMLE was considered most appropriate for the ROCKreal study due to its theoretical properties as an efficient double robust estimator and ability to adaptively adjust for many confounders [22,23]. TMLE first utilized machine learning to model the outcome regression, propensity score (PS), and outcome missingness mechanism (MM) using US data, then "targeted" (i.e., updated) the outcome regression to reduce bias in treatment effect estimates.

The targeted outcome regression model trained on US data was the basis for transporting the treatment effect to the European population [24]. Predicted outcomes were obtained for all European LOTs under treatment with belumosudil, $\hat{Y}_{BEL-EU}$, and under treatment with BAT, $\hat{Y}_{BAT-EU}$. Treatment-specific ORRs are obtained by averaging predicted outcomes over the European population, $\hat{ORR}_{BEL-EU} = \sum_{i=1}^{n-EU} \hat{Y}_{BEL-EU,i}$ and $\hat{ORR}_{BAT-EU} = \sum_{i=1}^{n-EU} \hat{Y}_{BAT-EU,i}$. The estimated ORR difference and ORR ratio are given by $\hat{ORR}_{DIFF-EU} = \hat{ORR}_{BEL-EU} - \hat{ORR}_{BAT-EU}$ and $\hat{ORR}_{RAT-EU} = \hat{ORR}_{BEL-EU} / \hat{ORR}_{BAT-EU}$, respectively. TMLE software produces standard error estimates, *P*-values, and confidence intervals that account for correlations among multiple LOTs contributed by the same patient [21].

Sensitivity transportability analysis

A sensitivity transportability analysis added standardizing weights to the US outcome regression model to enhance its prediction of outcomes in Europe. Inverse probability of study inclusion (IPS) weights, defined as the ratio of the conditional probabilities of being in Europe versus US LOT-level dataset, were incorporated into the TMLE analysis of US data to further tailor estimation towards the European population. IPS weights reflect each observation's contribution to fitting the outcome regression model. For example, US observations where the combination of characteristics were rarely observed in Europe data received a weight near 0 with minimal contribution to model fitting. US observations where characteristics were common in European patients received larger weights, thereby enhancing performance in predicting outcomes for European patients. In this way, this novel TMLE more aggressively adjusts for differences in the joint distribution of covariates in US and European patients [24]. Incorporating these weights improved outcome regression fitting for the European population and reduced bias in the effect estimate during the TMLE "targeting" step.

RESULTS

Study Population

Data on 350 cGVHD patients were collected from 32 European sites. 222 patients met eligibility criteria after applying the LOT algorithm to harmonize data across sites (Figure 2), including 106 patients from Spain (48%), 42 from France (19%), 40 from Italy (18%), and 34 from Great Britain (15%). These patients contributed a total of 363 qualifying LOTs; 123 patients contributed a single LOT, 64 patients contributed 2 LOTs, 28 patients contributed 3 LOTs, and 7 patients contributed 4 LOTs. Detailed information on the US cohort can be found in a previous publication [13].

BASELINE CHARACTERISTICS

Baseline characteristics at LOT initiation were generally well-balanced between European and US patients (Table 1). Any potential differences were adjusted for in the modeling step. More specifically, the characteristics are available in Table S3. Distributions of gender, transplant indication, transplant source, conditioning regimen and number of prior LOTs were similar. European patients were slightly younger with slightly lower weight and BMI than US patients. The reported median number of organs involved was 2 for European and 3 for US LOTs. The liver was more often involved in European versus US LOTs, while skin, eyes, lung, or muscles/joint/fascia were less often involved in European LOTs. Pulmonary complications of transplant and a second hematopoietic cell transplantation were more common in Europe, while depression/anxiety was less common than in the US. Matched-related or haploidentical donors were more common in Europe, with matched-unrelated donors less common than in the US. European LOTs were more likely to have a history of grade II–IV acute cGVHD, and have mild to moderate cGVHD compared to US LOTs.

The distribution of agents used immediately prior to LOTs included in our analysis appeared broadly similar between Europe and the US

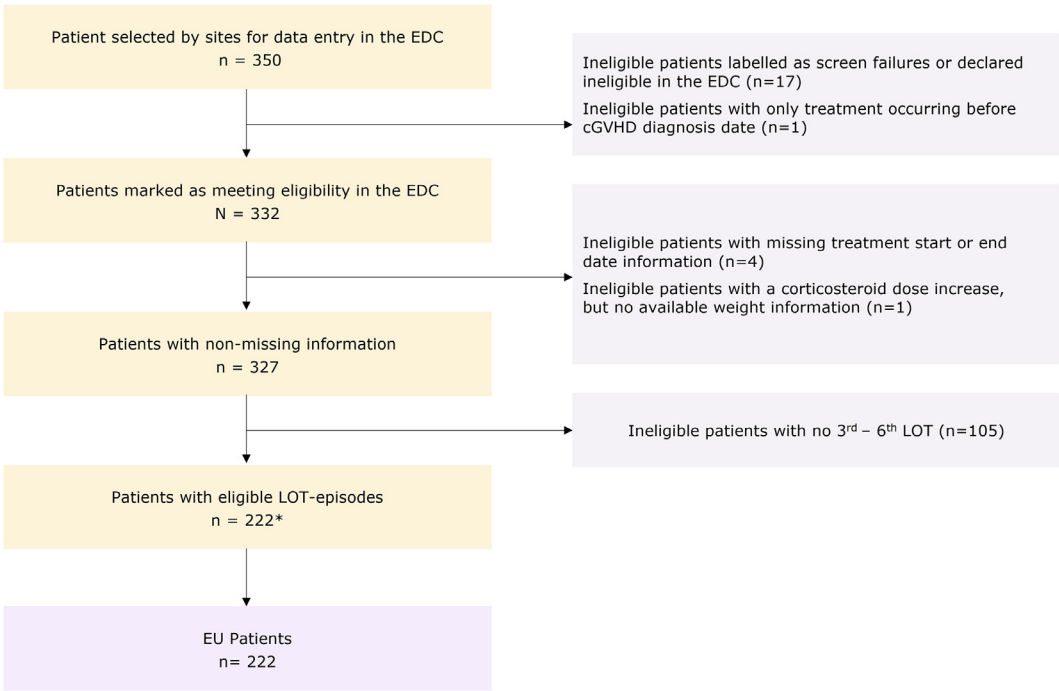

Figure 2. Consort diagram for patient selection from 32 Europe-based sites between August 20, 2023 and March 27, 2024. *Includes 8 pediatric patients.

(Figure S2). This likely reflects the heterogeneity in manifestation of the disease in the individual, with physicians relying on the same mix of agents—both licensed for use in cGVHD and used off-label. European patients were more likely to have received prior treatment with extracorporeal photopheresis, mycophenolate mofetil, imatinib, or cyclosporine, while US patients were more likely to have received rituximab, sirolimus, ruxolitinib, ibrutinib, tacrolimus, or CS. Prior treatment with ruxolitinib was present in 46% of US LOTs as compared with 34% of European LOTs.

Primary transportability analysis

Table 2 reports the estimated 6-month ORR for each treatment arm, ORR ratio and ORR difference between belumosudil and BAT in the European population, including standard errors, *P*-values, and 95% confidence intervals (CIs). Overall response was higher with belumosudil, estimated at 37.6%, as compared with 26.3% estimated for BAT. The ORR ratio of 1.42 (95% CI: [1.05, ∞); *P*-value = .03) indicates a 42.7% improvement with belumosudil compared to BAT, while the estimated ORR difference of 0.11 (95% CI: [0.08, 1);
P-value = .04) is a statistically significant finding of increased ORR in the European population when treated with belumosudil compared to BAT. For context, the proportion of LOT episodes classified as responders solely due to $\geq$50% corticosteroid taper was 8% in the ROCKreal study conducted for US population [13].

Sensitivity transportability analysis

The sensitivity transportability analysis incorporated IPS weights, defined as the ratio of the conditional probabilities of being in the European versus US LOT-level dataset, to enhance the prediction of outcomes in EU. IPS weights on US LOTs ranged from a minimum of 0.000025 to a maximum of 12.0 (mean = 1.0, median = 0.67). 99% of US LOTs had weights $<$5.9, indicating no observations were overly influential. The use of IPS weights and the ratio of the number of US LOTs to European LOTs (1.02) was applied to reduce bias in transporting the effect estimate to the European population, at a cost of increased variance.

Estimated 6-month ORR was again higher with belumosudil (40.2%) than with BAT (27.0%). The ORR difference between belumosudil and BAT in the European population was 0.13 (95% CI: [$-$0.04, 1.00); *P*-value = .10) and ORR ratio was 1.49 (95% CI: [0.93, ∞); *P*-value = .08). This analysis yielded results which were shifted away from the null slightly more than the primary transportability analysis, indicating a larger beneficial effect of belumosudil in European patients (Figure 3). However, due to the increased standard error,

Table 1
Baseline Characteristics of Eligible LOTs by European (n = 363) and US (n = 358) Populations

		Europe Population (n LOTs = 363)			US Population (n LOTs = 358)		
		Nonmissing, n	N, Mean, Median	%, (SD), [Q1, Q3]	Nonmissing, n	N, Mean, Median	%, (SD), [Q1, Q3]
Age at initiation of eligible LOT, years	Mean, SD	363	49.9	(14.3)	358	54.3	(16.1)
	Median, [Q1, Q3]		52.6	[42.5, 60.7]		57.6	[41.7, 67.2]
Age categories at initiation of eligible LOT, years	12 to <18	363	16	4%	358	3	1%
	18 to 65		301	83%		231	65%
	>65		46	13%		124	35%
Sex	Male	363	225	62%	358	210	59%
	Female		138	38%		148	41%
Number of prior LOTs	Mean, SD	363	2.5	(0.8)	358	2.7	(.9)
	Median, [Q1, Q3]		2	[2, 3]		2	[2,3]
	2 Prior LOTs		217	60%		188	53%
	3 Prior LOTs		102	28%		100	28%
	4 Prior LOTs		36	10%		54	15%
	5 Prior LOTs		8	2%		16	4%
Number of organs involved (prior to initiation of LOT)	Mean, SD	354	2.6	(1.3)	345	3.2	(1.3)
	Median, [Q1, Q3]		2	[2, 3]		3	[2, 4]
Type of organ involved (prior to initiation of LOT)	Skin	355	250	70%	349	267	77%
	Mouth		152	43%		156	45%
	Eyes		145	41%		220	63%
	GI Tract		68	19%		60	17%
	Liver		86	24%		57	16%
	Genitalia		30	8%		30	9%
	Lung		69	19%		120	34%
	Muscles/Joints/Fascia		107	30%		184	53%
	Other		16	5%		25	7%
	Missing		8	2%		9	3%
Graft source	Peripheral blood stem cells	363	336	93%	352	321	91%
	Marrow		18	5%		28	8%
	Cord blood		9	2%		3	1%
	Missing		0	0%		6	2%
Donor source/HLA matching	Matched-related donor	363	161	44%	358	109	30%

(*continued*)

Table 1 (*Continued*)

		Europe Population (n LOTs = 363)			US Population (n LOTs = 358)		
		Nonmissing, n	N, Mean, Median	%, (SD), [Q1, Q3]	Nonmissing, n	N, Mean, Median	%, (SD), [Q1, Q3]
	Matched-unrelated donor		128	35%		199	56%
	Mismatched-related donor		8	2%		4	1%
	Mismatched-unrelated donor		36	10%		30	9%
	Haploidentical		30	8%		16	4%
Conditioning regimen	Reduced intensity/nonmyeloablative	352	190	54%	358	201	56%
	Myeloablative		162	46%		157	44%
Donor gender match	Yes	345	180	52%	340	194	57%
	Missing		18	5%		26	7%
History of Grade II—IV aGVHD	Yes	325	172	53%	346	166	48%
	Missing		38	10%		12	3%
cGVHD severity (prior to initiation of LOT)	Mild	294	36	12%	327	26	8%
	Moderate		141	48%		133	41%
	Severe		117	40%		168	51%
	Missing		69	19%		31	9%
HCT-CI Score (prior to transplant)	0	162	16	4%	207	37	10%
	1–2		73	20%		93	26%
	≥3		73	20%		77	22%
	Missing		201	55%		151	42%

Missing values were excluded from proportion calculation.

US indicates United State; SD, standard deviation; Q1, quartile 1; Q3, quartile 3; LOT, line of therapy; HLA, human leukocyte antigen; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; BAT, best available therapy; BEL, Belumosudil; EU, Europe; GI, gastrointestinal.

Table 2
Primary Transportability Analysis Estimates, Standard Errors, *P*-Value, and 1-sided 95% Confidence Interval for the Rate Difference and Rate Ratio of Treatment With Belumosudil Versus BAT in the European Population

	Estimate	Standard Error	1-Sided *P*-Value	95% CI
BAT ORR	26.3%	0.031	<.001	[0.213, 1)
Belumosudil ORR	37.6%	0.055	<.001	[0.285, 1)
ORR Ratio	1.427	0.189	.030	[1.045, ∞)
ORR Difference	0.113	0.064	.039	[0.008, 1)

BAT indicates best available therapy; ORR, overall response rate; RD, rate difference; CI, confidence interval.

these findings did not reach statistical significance at the 5% level (Table S4).

DISCUSSION

Patients with cGVHD often require multiple LOTs due to disease progression and treatment intolerance, leading to significant morbidity and mortality [25]. Belumosudil, approved by the US FDA in 2021 for patients aged ≥12 years with cGVHD after failure of 2 to 5 prior LOTs, demonstrated efficacy in the ROCKstar trial [11]. While its use in Europe is limited to compassionate use programs, as of November 17, 2025, more than 1300 patients across 19 EU countries have received belumosudil after failure of existing approved therapies, highlighting the unmet need for effective and safe treatments in Europe. Real-world evidence on treatment with belumosudil in European patients with cGVHD is essential to assess its potential benefits in improving patient outcomes and reducing morbidity and mortality compared to best available therapies.

This initial study aimed to assess the potential safety and efficacy of belumosudil in European patients with cGVHD through transportability analysis of the real-world evidence generated in a US population. We first assessed the clinical and demographic characteristics of US and European patients with cGVHD who had failed 2 to 5 prior LOTs. Baseline characteristics were consistently collected in the US and Europe, revealing broad similarities between the 2 populations. The primary aim of the study was to conduct a transportability analysis to model the effect of belumosudil in European patients with cGVHD based on the real-world US treatment effects, assuming comparable biological responses which were confirmed taking into account, that the US cohort contained mainly Caucasian patients [14]. Consistent with the positive effects observed in the US, the primary transportability analysis indicated belumosudil would provide a clinically meaningful benefit for European cGVHD patients, with an ORR estimate of 37.6%, a 42.7% improvement over BAT. A sensitivity transportability analysis was

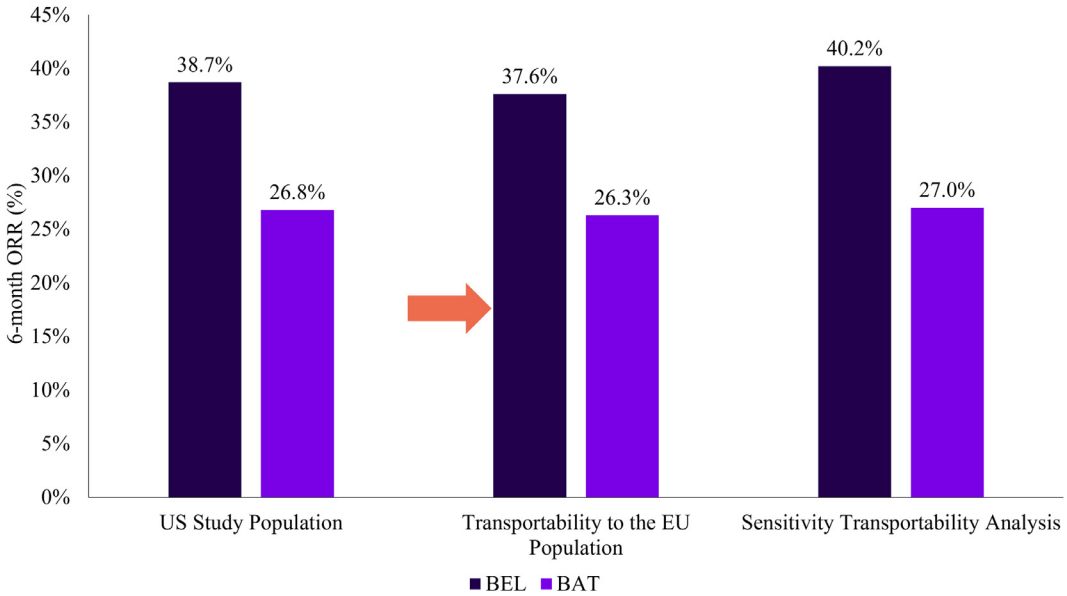

Figure 3. ORR comparison between US study population, the primary transportability analysis to the European population, and the sensitivity transportability analysis.

then conducted which employed a model trained on a weighted US dataset that more closely matched the European population. This sensitivity analysis also suggested a beneficial effect of belumosudil on European patients and a potentially even stronger effect than what was observed in the primary transportability analysis (6-month ORR of 40.2% versus 37.6% in the primary analysis).

The findings from this study align with evidence provided by a few recent single-arm, real-world studies evaluating belumosudil's efficacy in European patients. One retrospective, multicenter, chart review study in France reported a 6-month ORR of 45.6% with belumosudil, which closely aligns with the 6-month ORRs when treated with belumosudil in the primary and sensitivity analyses of the current study [26]. Two other multicenter retrospective analyses report a best ORR with belumosudil exceeding 40% and a single-center analysis reports a 6-month ORR of over 60%, reinforcing the positive clinical benefit expected with belumosudil use in real-world European patients [27–29]. Of note, the current study evaluates a European population larger than that included in these previous studies, was the first comparative study conducted in a real-world setting which analyzed the efficacy of belumosudil in comparison to BAT, and evaluates ORR at 6 months as opposed to best ORR. However, findings from each of these studies, including the current study, support the beneficial effect of treatment with belumosudil on response in European patients with cGVHD. Sustained steroid reduction is recognized as a clinically meaningful indicator of benefit in late-line cGVHD, consistent with prior work examining composite clinical benefit measures [20].

These findings have significant implications for clinical practice across Europe. Currently, European clinicians managing cGVHD patients who fail BAT face limited options, often resorting to treatments with suboptimal efficacy-to-toxicity profiles. The current transportability analysis provides compelling evidence that belumosudil could substantially improve outcomes for European patients, potentially reducing the burden of prolonged immunosuppression and its associated complications. The demonstrated 42.7% improvement in 6-month ORR over BAT suggests that broader access to belumosudil could transform treatment algorithms for refractory cGVHD in Europe. Additionally, the comparable efficacy between US and European populations supports harmonization of treatment guidelines across regions. For European clinicians, these results contribute to the scientific evidence base regarding outcomes in patients who have exhausted standard therapies, highlighting the potential impact on treatment sequencing and the cumulative burden of toxicities in this challenging patient population.

Key strengths of this transportability analysis include simultaneous collection of fit-for-purpose data in both the US and European populations, use of the same LOT algorithm across US and European sites, and the application of TMLE to address challenges in estimating the treatment effect in RWD. Information on 30 potential baseline confounders, including underlying malignancy, transplant type, comorbidities, and prior therapies was used to transport findings from the US to European population. This analysis, one of the few comparing US and European patients independent of specific treatments received, supports the conclusion that patients with cGVHD show comparable outcomes in both regions.

This study addressed the challenges of evaluating treatment effects with RWD through careful study design and application of rigorous statistical methodologies for causal inference. However, a few limitations inherent to RWD and assumptions required to conduct transportability of effect estimates from the US source population to the European target population need to be considered.

Despite comprehensive and diligent quality assurance efforts, primary data collection can result in varying levels of missingness of outcomes and key confounders. This left the potential for unmeasured confounders, one of the key assumptions underlying the validity of causal inference analysis. The methodology of this study assumes that, given the same clinical characteristics and treatment history, the effect of treatment with belumosudil or BAT on a patient's outcome would be the same whether the patient was from the US or Europe. Differences between the US source and European target populations in characteristics, setting, treatment timing or dosage, and timing of outcome measurements, were addressed via consistent data collection across US and European sites; however, variation in the probability of enrollment in the study between US and European patients may still be present [16,30]. While most covariates were well-balanced between the US and European populations a limitation of both populations was the relatively small number of pediatric patients. Additionally, some confounders such as flare history, exact steroid dosing, and organ-specific NIH measures may

have had some missing data. Thus, it remains unclear whether the observed outcomes and treatment effects are applicable to pediatric patients receiving treatment in the real-world. Further research specifically targeting the efficacy and safety of belumosudil for pediatric patients is needed to address this gap and provide more robust evidence. Specific to the sensitivity transportability analysis, one limitation was that the model implemented required a more aggressive approach based on the overlap in US and European patient characteristics and the ratio of the number of US LOTs to European LOTs. The larger beneficial effect of belumosudil in the European population, indicated by this sensitivity analysis, did not reach statistical significance at the 5% level due to the increased standard error.

Similar to the positive effect observed in the US and European patients in other real-world evidence studies, findings from this transportability analysis indicate that treatment with belumosudil would benefit cGVHD patients in Europe as compared to BAT.

LIMITATIONS

European outcomes, including overall response and 12-month failure-free survival (FFS), were not captured in this study; therefore, survival endpoints could not be directly estimated for the European cohort. As a result, all efficacy estimates for Europe reflect transported predictions derived from US outcome models rather than observed European clinical data, precluding evaluation of whether the treatment effect observed in the US ROCKreal study extends to longer-term outcomes such as FFS in European patients.

In addition, the composite 6-month ORR incorporated both NIH-defined complete or partial responses (CR/PR) and steroid-sparing clinical benefit through $\geq$50% corticosteroid taper without progression. These components differ in clinical interpretation: NIH-defined CR/PR reflects organ-specific response, whereas steroid reduction represents meaningful symptomatic and toxicity-related improvement in late-line cGVHD. Both metrics were reported to provide transparency regarding the distinct dimensions of clinical benefit captured by the composite endpoint.

INSTITUTIONAL REVIEW BOARD APPROVAL

IRB approval was obtained from all participating sites, namely Ethics Committee of the Faculty of Medicine—Justus-Liebig-Universität Giessen, Health Research Authority, CET Sicily—A.O.U.P, Ethics Committee of the Emilia Central Wide Area (AVEC), CET Lazio Area 2, CET Marche, Territorial ethics committee Calabria region, Ethics Committee of the Tuscany Region – Central Vast Area, Niño Jesús Children's University Hospital, Regional University Hospital of Malaga, Ethics Committee for Research with Medicines - CEIm Hospital Clínico Universitario de Valencia, Bellvitge University Hospital, Ethics Committee for Research with Medicines of the Principality of Asturias, Puerta de Hierro Majadahonda University Hospital, Ethics Committee for Research with Medicines of Euskadi, La Paz University Hospital, Office of Research Administration Emory University, Institutional Review Board Office Augusta University, Health Center Institutional Review Board, 6100 Merriweather Dr., Suite 600, University of California, Fred Hutchinson Cancer Research Center. Due to the retrospective study design, if possible as per local regulation, Informed Consent waivers were requested for adults over 18 years of age. If not possible as per local regulation, participating patients signed an ICF.

AGREEMENT TO SHARE PUBLICATION-RELATED DATA

Qualified researchers may request access to deidentified patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

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SUPPLEMENTARY MATERIALS

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REFERENCES

1. Gonzalez RM, Pidala J. Evolving therapeutic options for chronic graft-versus-host disease. *Pharmacotherapy*. 2020;40(8):756–772.
2. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med*. 2021;385(3):228–238.
3. Henden AS, Hill GR. Cytokines in graft-versus-host disease. *J Immunol*. 2015;194(10):4604–4612.
4. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*. 2015;125(4):606–615.
5. Wolff D, Fatobene G, Rocha V, et al. Steroid-refractory chronic graft-versus-host disease: treatment options and patient management. *Bone Marrow Transplant*. 2021;56:2079–2087.

6. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood*. 2017;130:2243–2250.
7. Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *Lancet Haematol*. 2020;7(2):e157–e167.
8. Denk A, Alexander Fante M, Heidenreich S, et al. Changes in chronic graft-versus-host disease treatment over time: a 15-years survey within allogeneic hematopoietic stem cell transplant centers in Germany, Austria, and Switzerland. *Transplant Cell Ther*. 2025. https://doi.org/10.1016/j.jtct.2025.04.017.
9. 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.
10. 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.
11. Cutler C, Lee SJ, Arai S, et al. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study [published correction appears in Blood. 2022 Mar 17;139(11):1772. 10.1182/blood.2022015598]. *Blood*. 2021;138(22):2278–2289.
12. Wolff D, Cutler C, Lee SJ, et al. Axatilimab in recurrent or refractory chronic graft-versus-host disease. *N Engl J Med*. 2024;391(11):1002–1014.
13. Hall K, Lazaryan A, van der Laan M, et al. Efficacy and safety of belumosudil as compared with best available therapy for the treatment of cGVHD in the US. *Blood Adv*. 2025. https://doi.org/10.1182/bloodadvances.2025015832.
14. Inoue K, Hsu W. Transportability analysis—a tool for extending trial results to a representative target population. *JAMA Netw Open*. 2024;7(1):e2346302.
15. Turner AJ, Sammon C, Latimer N, et al. Transporting comparative effectiveness evidence between countries: considerations for health technology assessments. *PharmacoEconomics*. 2024;42:165–176.
16. Degtiar I, Rose S. A review of generalizability and transportability. *Annu Rev Stat Appl*. 2023;10(1):501–524.
17. Rudolph KE, van der Laan MJ. Robust estimation of encouragement-design intervention effects transported across sites. *JR Stat Soc Series B Stat Methodol*. 2017;79(5):1509–1525.
18. Wolff D, Cutler C, Mercep I, et al. Towards better and more effective clinical trials for Chronic Graft-versus-host disease. *Transplant Cell Ther*. 2025. https://doi.org/10.1016/j.jtct.2025.11.008.
19. European Medicines Agency. *Reflection Paper on Use of Real-WORLD Data in Noninterventional Studies to Generate Real-world Evidence for Regulatory Purposes*. Amsterdam: EMA; 2025. Available from: RWE Reflection paper - final version for publication .
20. White J, Elemary M, Linn SM, et al. A multicenter, retrospective study evaluating clinical outcomes of ruxolitinib therapy in heavily pretreated chronic GVHD patients with steroid failure. *Transplant Cell Ther*. 2023;29(2):120.e1–120.e9.
21. Van der Laan M, Rose S. *Targeted Learning in Data Science: Causal Inference for Complex Longitudinal Studies*. Cham, Switzerland: Springer International Publishing; 2018.
22. Van der Laan M, Rose S. *Targeted Learning: Causal Inference for Observational and Experimental Data*. New York: Springer; 2011.
23. Van der Laan M, Rubin D. Targeted maximum likelihood learning. *Int J Biostat*. 2006;2(1):1–38.
24. Van der Laan M and Gruber S Technical note: targeted maximum likelihood estimator for an ATE standardized for new target population (2025). https://doi.org/10.48550/arXiv.2501.06381.
25. Langer R, Lelas A, Rittenschober M, et al. Retrospective analysis of the incidence and outcome of late acute and chronic graft-versus-host disease-an analysis from transplant centers across Europe. *Front Transplant*. 2024;3:1332181.
26. Michonneau D, Malard F, Le Grand S, et al. Efficacy and safety of belumosudil for treatment of cGVHD: multicenter retrospective analysis of the French cohort of the compassionate use program, on behalf of the French Society of Bone Marrow Transplantation and Cellular Therapy. *Bone Marrow Transplant*. 2025. https://doi.org/10.1038/s41409-025-02554-w.
27. Heidenreich S, Egger-Heidrich K, Halter JP, et al. Safety and efficacy of the ROCK-2-inhibitor Belumosudil in cGvHD treatment: a retrospective, German-Swiss multicenter real-world data analysis. *Bone Marrow Transplant*. 2025;60(4):439–446. https://doi.org/10.1038/s41409-024-02507-9.
28. Bailen R, Peña-Muñoz A, Bermúdez A, et al. Spanish real world experience (GETH-TC) of belumosudil for chronic graft-versus-host-disease after 2 or more prior lines of therapy. *EBMT 51st Annual Meeting*. Florence, Italy; 2025. https://ebmt2025.abstractserver.com/program/#/details/presentations/1798.
29. Bonifazi F, Roberto M, Lupo-Stanghellini MT, et al. *Italian retrospective real-life analysis on belumosudil for treatment-resistant/refractory chronic GVHD. EHA 30th Congress*. Milan, Italy; 2025. https://library.ehaweb.org/eha/2025/eha2025-congress/4161116/francesca.bonifazi.italian.retrospective.real-life.analysis.on.belumosudil.for.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dbelumosud.
30. Levy NS, Arena PJ, Jemielita T, et al. Use of transportability methods for real-world evidence generation: a review of current applications. *J Comp Eff Res*. 2024;4. https://doi.org/10.57264/cer-2024-006.