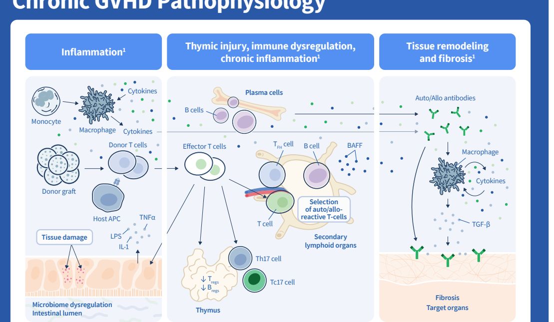
Clinical Considerations for the Use of Axatilimab-csfr for the Treatment of Chronic GVHD

Chronic GVHD Pathophysiology



The pathophysiology of chronic GVHD occurs in three phases:[1]

- Inflammation: Activated macrophages secrete pro-inflammatory cytokines. Donor T cells recognize host APCs, triggering alloimmune activation. Tissue damage reinforces local inflammation
- Immune dysregulation: Thymic damage impairs tolerance, leading to autoreactive T- and B-cell expansion and sustained inflammatory signaling
- Fibrosis: Activated macrophages (driven by IL-17 and CSF-1) produce profibrotic mediators, promoting fibroblast activation and tissue fibrosis

Activated Macrophages:

- Secrete cytokines to trigger early inflammation[2]
- Regulate tissue repair and remodeling[1,3]
- Depend on CSF-1 for development, function, and survival[2-4]
- Produce TGF-β and PDGF, resulting in fibroblast activation and chronic GVHD manifestations such as scleroderma or bronchiolitis obliterans[3]

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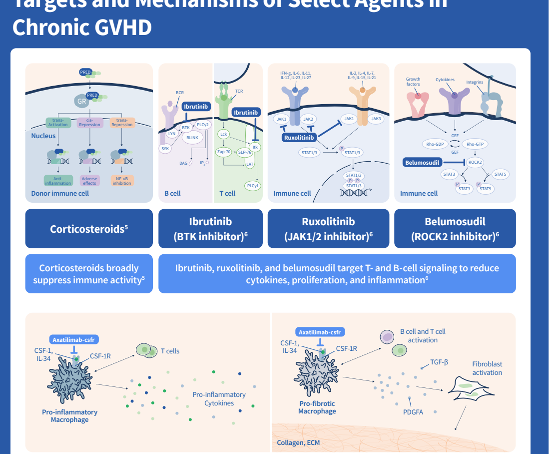
APC, antigen presenting cell; ASH, American Society of Hematology; Auto, autologous; BAFF, B cell activating factor; CSF-1, colony stimulating factor 1; IL-1, interleukin 1; GVHD, graft-versus-host disease; LPS, lipopolysaccharide; PDGF, platelet derived growth factor; TLR, toll-like receptor; Tc17, IL-17 secreting CD8 T cells; T_H cell, T helper cell; TGF-β, transforming growth factor beta; Th17, T helper 17; TNFα, tumor necrosis factor alpha.

Targets and Mechanisms of Select Agents in Chronic GVHD



BCR, B cell receptor; BLNK, B cell linker protein; BTK, Bruton's tyrosine kinase; CSF-1R, colony stimulating factor 1 receptor; DAG, diacylglycerol; ECM, extracellular matrix; GEF, guanine nucleotide exchange factor; GR, glucocorticoid receptor; GRE, glucocorticoid response element; IFN, interferon; IL, interleukin; IP3, inositol 1,4,5-trisphosphate; ITK, IL-2-inducible T cell kinase; JAK, Janus kinase; LAT, linker for activation of T cells; Lck, lymphocyte-specific protein tyrosine kinase; LYN, Lyn kinase; NF-κB, nuclear factor kappa B; PDGFA, platelet-derived growth factor subunit A; PLCγ, phospholipase C gamma; Rho-GTP, Rho-GDP, inactive GDP-bound form of Rho GTPase; Rho-GTP, active GTP-bound form of RhoA; ROCK2, Rho-associated coiled-coil containing protein kinase 2; SLP-76, SH2 domain-containing leukocyte protein of 76 kDa; STAT, signal transducers and activators of transcription; SYK, spleen tyrosine kinase; TCR, T cell receptor; TGF-β, transforming growth factor beta; Zap-70, zeta-chain-associated protein kinase 70.

Axatilimab-csfr Indication[9]

NIKTIMVO™ (axatilimab-csfr) is a colony stimulating factor-1 receptor-blocking antibody indicated for the treatment of chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg

Please see the Full Prescribing Information, including Warnings & Precautions, and Patient Information

AGAVE-201 Overview[9]

Study Design[9-12]

An open-label, randomized, phase 2 study of axatilimab-csfr in in 241 patients with chronic GVHD

Select Eligibility Criteria

- ≥2 years of age
- Active chronic GVHD
- ≥2 prior systemic therapies
- Use of agents other than corticosteroids or a CNI/mTOR inhibitor was prohibited

Treatment Regimen

Patients were randomized to receive one of three doses of axatilimab-csfr: 0.3 mg/kg q2w, 1.0 mg/kg q2w, and 3.0 mg/kg q4w

Treatment continued for up to 2 years *or until disease progression or unacceptable toxicity*

35% of patients received no corticosteroids during the study

Patients with severe lung involvement were eligible for enrollment

Patients with sustained responses on the q2w dosing schedule could transition to q4w dosing

Based on the results of the AGAVE-201 study, the US Food and Drug Administration approved axatilimab-csfr at the 0.3 mg/kg q2w dose

Efficacy Overview[10-12]

0.3 mg/kg q2w Cohort

Primary Endpoint: Overall Response Rate

74% Responded to axatilimab-csfr

59 of 80 patients in this cohort had a response

Time to Response

Median time to response was 1.7 months (range 0.9-8.1)

Duration of Response

60% of responses were maintained for **≥12 months** (95% CI 43-74)[a]

[a] Based on Kaplan-Meier estimate of 12-month event-free probability.

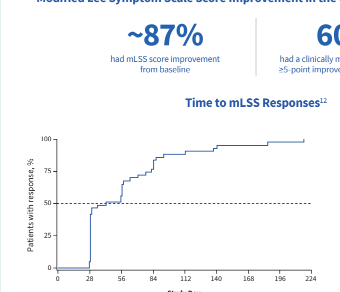
GVHD Symptom Improvement and Organ-Specific Responses With Axatilimab-csfr

Modified Lee Symptom Scale Score Improvement in the 0.3 mg/kg q2w Cohort[10,11]

~87% had mLSS score improvement from baseline

60% had a clinically meaningful change of ≥5-point improvement in mLSS score

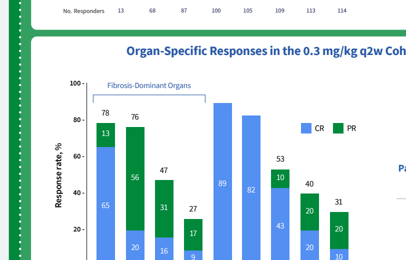
Time to mLSS Responses[12]

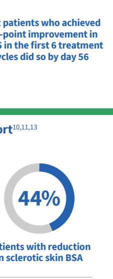


1.7 months Median time to ≥5-point improvement in mLSS score

Most patients who achieved a ≥7-point improvement in mLSS in the first 6 treatment cycles did so by day 56

Organ-Specific Responses in the 0.3 mg/kg q2w Cohort[10,11,13]





Patients with reduction in sclerotic skin BSA

Patients with improvement in skin and joint tightening

Responses were observed across all organs, including in the organs that had the most fibrotic changes[11]

Some symptoms of the lungs, mouth, eyes, and skin improved more rapidly by mLSS[a] than the corresponding NIH 2014 organ-specific response criteria[12]

Lung-specific responses were observed among patients with more severe disease at baseline (lung symptom score of 3, FEV_1 ≤39%)[b]

Analysis includes all patients who achieved both an organ-specific response by NIH 2014 consensus criteria and a symptom improvement in the corresponding organ in the first 6 cycles. Differences in percentage totals are due to rounding.
[a] ≥1-point improvement in individual mLSS symptoms. [b] ≥7-point improvement from baseline in mLSS.
BSA, body surface area; CR, complete response; FEV_1, forced expiratory volume in 1 second; GI, gastrointestinal; mLSS, modified Lee Symptom Scale; NIH, National Institutes of Health; PR, partial response; TTR, time to response.

Effects of Prior Lines of Therapy in Patients Receiving Axatilimab-csfr[15]

ORR by last LOT

Across all doses

62% Patients treated with ruxolitinib in last LOT (n=68)

50% Patients treated with belumosudil in last LOT (n=34)

ORRs were consistent with axatilimab-csfr regardless of the number of prior LOT received

Organ-specific responses by last LOT

Across all doses

Ruxolitinib in last LOT showed a trend of higher responses in select organs vs belumosudil[a]

Joints/Fascia | Mouth | Lungs | Eyes | Skin

Organ-specific responses to axatilimab-csfr were noted regardless of last prior therapy[a]

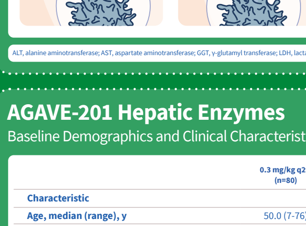
[a] Analyses were not powered to evaluate statistical differences. [b] Owing to low patient numbers when assessing the single-dose cohort of 0.3 mg/kg q2w, organ-specific response rates were assessed across all doses.

Overall Summary of TEAEs[16]

Variable, n (%)	0.3 mg/kg q2w (n=79)
Patients with TEAE	76 (96.2)
Grade ≥3	39 (49.4)
Serious TEAE	30 (38.0)
Patients with TRAE[a]	56 (70.9)
Grade ≥3	14 (17.7)
Serious TRAE	7 (8.9)
Patients with fatal TEAE[b]	1 (1.3)
Patients with TEAE leading to dose interruption[c]	30 (38.0)
Patients with TEAE leading to dose reduction	5 (6.3)
Patients with TEAE leading to treatment discontinuation	5 (6.3)
Patients with TEAE of special interest[d]	54 (68.4)
Grade ≥3	20 (25.3)

Safety population includes all patients who received ≥1 dose of axatilimab-csfr.
[a] TRAEs are TEAEs judged as related by the investigator or with a missing causality. [b] Dyspnea. [c] The most common TEAEs leading to dose interruption by system organ class were infections, hepatic enzyme elevations, CPK elevations, periorbital edema, and amylase and lipase elevations. [d] Infusion-related reactions (including hypersensitivity reactions), infections, tissue ulcerations, which were determined based on the drug class and mechanism of action of axatilimab-csfr.
CPK, creating phosphokinase; q2w, every 2 weeks; q4w, every 4 weeks; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Effects of CSF-1R Inhibition on Liver Isoenzymes[17]



- CSF-1 supports the differentiation and survival of Kupffer cells, the resident macrophages of the liver, which clear enzymes from daily tissue turnover, maintaining stable serum levels
- Axatilimab-csfr inhibits CSF-1R, reducing Kupffer cells and impairing the clearance of enzymes such as AST, ALT, CPK, LDH, GGT, amylase, and lipase
- In preclinical models, resulting serum enzyme elevations reflected reduced macrophage-mediated clearance and were not accompanied by evidence of hepatic or skeletal muscle injury

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; LDH, lactate dehydrogenase.

AGAVE-201 Hepatic Enzymes

Baseline Demographics and Clinical Characteristics[17]

	0.3 mg/kg q2w (n=80)	1.0 mg/kg q2w (n=81)	3.0 mg/kg q4w (n=80)
Characteristic			
Age, median (range), y	50.0 (7-76)	56.0 (26-81)	53.0 (7-79)
Male, n (%)	47 (58.8)	51 (63.0)	53 (66.3)
cGVHD in liver, n (%)	10 (12.5)	13 (16.0)	17 (21.3)
Conditioning regimen, n (%)			
Myeloablative	55 (66.8)	57 (70.4)	47 (58.8)
Nonmyeloablative	24 (30.0)	24 (29.6)	32 (40.0)
Other	1 (1.3)	0	1 (1.3)
Patients with elevated laboratory values at baseline, n/N (%)[a]			
AST	10/79 (12.7)	16/81 (19.8)	24/79 (30.4)
ALT	9/79 (11/4)	16/81 (19.8)	26/79 (32.9)
ALP	15/79 (19.0)	19/80 (23.8)	27/77 (35.1)
Total bilirubin	1/77 (1.3)	0	3/78 (3.8)
Amylase	5/77 (6.5)	12/78 (15.4)	11/74 (14.9)
Lipase	4/79 (5.1)	2/80 (2.5)	6/75 (8.0)
CPK	6/77 (7.8)	12/80 (15.0)	2/76 (2.6)
LDH	46/79 (58.2)	39/81 (48.1)	39/77 (50.6)
GGT	45/78 (57.7)	40/81 (49/4)	53/77 (68.8)

[a] Includes patients in safety analysis set (0.3 mg/kg q2w, n=79; 1 mg/kg q2w, n=80; 3 mg/kg q4w, n=79; baseline patient counts vary per LFT).
LFT, liver function test; ULN, upper limit of normal.

Eligible patients had baseline ALT/AST ≤2.5 × ULN (≤5 × ULN with liver cGVHD) and total bilirubin ≤1.5 × ULN

Incidence[17]

	0.3 mg/kg q2w (n=79)		1.0 mg/kg q2w (n=81)		3.0 mg/kg q4w (n=79)	
Preferred term, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Laboratory-based TEAEs						
AST increased	11 (13.9)	1 (1.3)	31 (38.3)	1 (1.2)	43 (54.4)	3 (3.8)
ALT increased	10 (12.7)	1 (1.3)	18 (22.2)	2 (2.5)	31 (39.2)	2 (2.5)
ALP increased	5 (6.3)	0	4 (4.9)	0	17 (21.5)	0
Bilirubin increased	1 (1.3)	0	0	0	1 (1.3)	0
Amylase increased	3 (3.8)	0	10 (12.3)	1 (1.2)	34 (43.0)	2 (2.5)
Lipase increased	9 (11.4)	1 (1.3)	21 (25.9)	1 (1.2)	39 (49.4)	4 (5.1)
CPK increased	9 (11.4)	1 (1.3)	26 (32.1)	6 (7.4)	49 (62.0)	12 (15.2)
GGT increased	8 (10.1)	1 (1.3)	16 (19.8)	2 (2.5)	21 (26.6)	4 (5.1)
TEAEs leading to dose interruption	2 (2.5)	1 (1.3)	7 (8.6)	5 (6.2)	7 (8.9)	6 (7.6)
AST increased	1 (1.3)	1 (1.3)	3 (3.7)	1 (1.2)	2 (2.5)	2 (2.5)
ALT increased	1 (1.3)	1 (1.3)	3 (3.7)	1 (1.2)	1 (1.3)	1 (1.3)
Amylase increased	1 (1.3)	0	0	0)	2 (2.5)	1 (1.3)
Lipase increased	1 (1.3)	0	0	0	3 (3.8)	2 (2.5)
CPK increased	0	0	3 (3.7)	3 (3.7)	2 (2.5)	2 (2.5)
GGT increased	0	0	1 (1.2)	1 (1.2)	1 (1.3)	0
TEAEs leading to dose reduction	1 (1.3)	0	3 (3.7)	3 (3.7)	3 (3.8)	1 (1.3)
AST increased	0	0	0	0	1 (1.3)	1 (1.3)
ALT increased	1 (1.3)	0	0	0	1 (1.3)	1 (1.3)
CPK increased	0	0	2 (2.5)	2 (2.5)	2 (2.5)	0
GGT increased	0	0	1 (1.2)	1 (1.2)	0	0
TEAEs leading to study drug discontinuation	0	0	0	0	0	0

ALP, alkaline phosphatase.

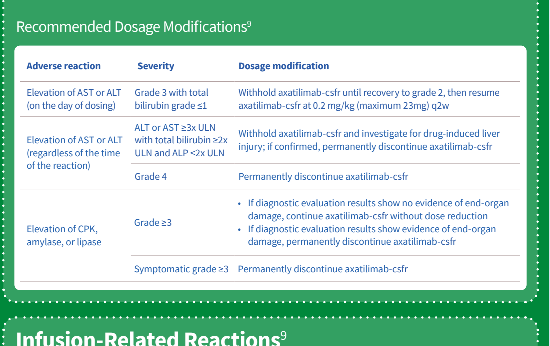
The most common TEAEs were increased levels of AST, ALT, CPK, lipase, and amylase

Laboratory-based TEAEs were less frequent with 0.3 mg/kg q2w compared with higher doses, with individual grade ≥3 TEAEs occurring in <2% of patients in the 0.3 mg/kg q2w group

Across all doses, no patients discontinued treatment owing to laboratory-based TEAEs

Dynamics[13,17]

Mean Levels in Patients Treated With Axatilimab-csfr 0.3 mg/kg q2w During the First 10 Treatment Cycles (Required Visits Only)



AST, ALT, ALP, CPK, amylase, and lipase should be monitored prior to the start of treatment with axatilimab-csfr, every 2 weeks for the first month, and every 1 to 2 months thereafter until abnormalities are resolved

Elevations in hepatic laboratory values, known on-target effects of CSF-1R inhibition, occurred without accumulation during continued treatment

Laboratory-based TEAEs were primarily:

- **Transient**
- **Plateauing or returning to near baseline**
- **Grade 1/2**
- **Requiring few dose changes**
- **Not resulting in treatment discontinuation**

Recommended Dosage Modifications[9]

Adverse reaction	Severity	Dosage modification
Elevation of AST or ALT (on the day of dosing)	Grade 3 with total bilirubin grade ≤1	Withhold axatilimab-csfr until recovery to grade 2, then resume axatilimab-csfr at 0.2 mg/kg (maximum 23mg) q2w
Elevation of AST or ALT (regardless of the time of the reaction)	ALT or AST >3x ULN with total bilirubin ≥2x ULN and ALP <2x ULN	Withhold axatilimab-csfr and investigate for drug-induced liver injury; if confirmed, permanently discontinue axatilimab-csfr
	Grade 4	Permanently discontinue axatilimab-csfr
Elevation of CPK, amylase, or lipase	Grade ≥3	• If diagnostic evaluation results show no evidence of end-organ damage, continue axatilimab-csfr without dose reduction • If diagnostic evaluation results show evidence of end-organ damage, permanently discontinue axatilimab-csfr
	Symptomatic grade ≥3	Permanently discontinue axatilimab-csfr

Infusion-Related Reactions[9]

Recommended Dosage Modifications[9]

Adverse reaction	Severity	Dosage modification
Infusion-related reactions	Grade 1 or 2	• Temporarily interrupt the infusion until resolution or decrease the infusion rate by 50% • Initiate symptomatic treatment (eg, antihistamines and antipyretics) • For subsequent infusions, premedicate and resume the infusion at 50% of the prior infusion rate
	Grade 3 or 4	• Permanently discontinue axatilimab-csfr

Infusion-related reactions, including hypersensitivity reactions, occurred in 18% of all patients who received axatilimab-csfr in AGAVE-201, with grade 3 or 4 reactions in 1.3%

Patients who have previously experienced an infusion-related reaction to axatilimab-csfr should be premedicated with an antihistamine and an antipyretic and monitored for signs and symptoms of infusion-related reactions, including fever, chills, rash, flushing, dyspnea, and hypertension; interrupt or slow the rate of infusion or permanently discontinue axatilimab-csfr based on severity of the reaction

Cytopenias[13,16]

Grade ≥3 Hematologic Abnormalities

Among all cohorts in AGAVE-201 (N=239)

Blood and lymphatic system disorders:	4.2%
Anemia	2.1%
Febrile neutropenia	0.4%
Immune thrombocytopenia	0.4%
Neutropenia	1.3%
Thrombocytopenia	0.8%

The most common cytopenia was anemia, which occurred in 10 (12.7%), 6 (7.4%), and 10 (12.7%) patients in the 0.3mg/kg q2w, 1 mg/kg q2w, and 3 mg/kg q4w cohorts, respectively

Infections[11,13,16]

	Axatilimab-csfr 0.3 mg/kg q2w (n=79)	Total (N=239)
Any grade infections	58 (73.4)	172 (72.0)
Viral infections		
BK virus infection	1 (1.3)	1 (0.4)
COVID-19	13 (16.5)	42 (17.6)
COVID-19 pneumonia	3 (3.8)	3 (1.3)
Coronavirus infection	2 (2.5)	3 (1.3)
Cytomegalovirus infection	0 (0)	1 (0.4)
Cytomegalovirus infection reactivation	0 (0)	1 (0.4)
Epstein-Barr virus	0 (0)	1 (0.4)
Epstein-Barr virus infection	0 (0)	2 (0.8)
Epstein-Barr virus infection reactivation	0 (0)	1 (0.4)
Fungal infections		
Aspergillus infection	0 (0)	1 (0.4)
Bronchopulmonary aspergillosis	0 (0)	2 (0.8)
Candida infection	3 (3.8)	9 (3.8)

BK virus, human polyomavirus 1; CMV, cytomegalovirus; COVID-19, coronavirus disease of 2019; EBV, Epstein-Barr virus.

Clinically significant opportunistic infections were rare with axatilimab-csfr at the FDA-approved 0.3 mg/kg q2w dose

No CMV, EBV, or invasive fungal infections occurred in patients who received axatilimab-csfr at 0.3 mg/kg every q2w

Summary

- Chronic GVHD has inflammatory and fibrotic manifestations involving CSF-1R-dependent monocytes and macrophages[1-4]
- Therapeutic agents for chronic GVHD target immune cells by blocking cytokine and growth factor signaling or by depleting proinflammatory myeloid cells[5-8]
- Axatilimab-csfr targets CSF-1R to inhibit the activity of monocytes and macrophages that contribute to chronic inflammation and tissue fibrosis in chronic GVHD[6-8]
- In AGAVE-201, 74% of patients receiving axatilimab-csfr 0.3 mg/kg q2w had a clinical response, and responses were noted in all fibrosis-dominant organs[10,11]
- In the 0.3 mg/kg q2w cohort, 60% of patients achieved a clinically meaningful ≥5-point mLSS reduction within the first 6 cycles[11]
- The most common TEAEs were increased levels of AST, ALT, CPK, lipase, and amylase[13]
- Elevations in hepatic laboratory values occurred without accumulation during continued treatment and were primarily transient[17]
- Infusion-related reactions occurred in 18% of patients who received axatilimab-csfr in AGAVE-201, with grade 3 or 4 reactions in 1.3%[9]
- In the 0.3 mg/kg q2w cohort, anemia was the most common cytopenia observed (12.7% of patients), while invasive fungal infections and opportunistic infections were not observed[16]

Warnings and Precautions[9]

Infusion-Related Reactions: Premedicate patients with an antihistamine and antipyretic if they have previously had an infusion-related reaction, and monitor for symptoms such as fever, chills, rash, flushing, dyspnea, and hypertension, adjusting or discontinuing the infusion based on severity

Embryo-Fetal Toxicity: Axatilimab-csfr may cause fetal harm due to its mechanism of action; verify pregnancy status and advise pregnant women and people of reproductive potential of this risk and instruct use of effective contraception during treatment and for 30 days after the last dose

Lactation: Advise women not to breastfeed during treatment and for 30 days after the last dose of axatilimab-csfr

Pediatric Use: Safety and efficacy are not established for those weighing <40kg; based on findings of thickening of the growth plate and metaphysis and/or degeneration of the growth plate in the femur in animals, monitor bone growth and development in pediatric patients (<40kg)

Geriatric Use: No overall differences in the safety and efficacy of axatilimab-csfr have be observed between patients ≥ 65 years and younger patients

1. Hamilton BK. Hematology Am Soc Hematol Educ Program. 2021;2021(1):648–654. 2. Hong YQ, et al. World J Clin Cases. 2020;8(9):1793-1805. 3. Alexander KA, et al. J Clin Invest. 2014;124:4266–4280. 4. Hume DA, MacDonald KP. Blood. 2012;119:1810-1820. 5. Kasenda S et al. Orphanet J Rare Dis. 2021;16:12. 6. Lee SJ, and Zeiser R. Blood. 2024 Feb 29;143(9):790-800. 7. Cerroni M et al. Cancers (Basel). 2024;16:115. 8. Kitko CL, et al. J Clin Oncol. 2023;41:1864-1875. 9. NIKTIMVO™ (axatilimab-csfr). Prescribing information. Incyte Corporation; January 2025. 10. Wolff D, et al. Presentation at ASH Annual Meeting. December 10, 2023. 11. Wolff D, et al. N Engl J Med. 2024;391(1062-1074). 12. Chen H, et al. ASH 2024. Abstract 98. 13. Data on File. Incyte Corporation. 14. Salhotra A, et al. Am J Respir Crit Care Med. 2025;211:A5236. 15. Kitko CL, et al. Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR 2025. Abstract 387. 16. Diaz X, et al. HOPA 2025. Abstract TR 342. 17. Chen H, et al. Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR. February 2025. Abstract 399.

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