MINDway: A Phase Ib/II dose optimization study to assess safety and pharmacokinetics of tafasitamab + lenalidomide in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL)

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Background

- Currently, first-line standard of care for diffuse large B-cell lymphoma (DLBCL) comprises six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy[1]
- While R-CHOP is curative in 60–70% of patients,[2,3] 30–40% experience a relapsed/refractory (R/R) disease course[3,4]
 - Salvage therapy for R/R DLBCL includes high-dose chemotherapy and autologous stem cell transplant (ASCT)[1]
 - Patients are often ineligible for intensive treatment due to advanced age or comorbidities,[4,5] and approximately 40–65% relapse after ASCT[6–8]
- Tafasitamab, a humanized, Fc-modified, anti-CD19 monoclonal antibody, in combination with the immunomodulatory drug lenalidomide (LEN), demonstrated efficacy in the single-arm, Phase II L-MIND study (NCT02399085), in ASCT-ineligible patients with R/R DLBCL[9,10]
- The immunotherapy tafasitamab + LEN has been granted accelerated approval in the United States (July 2020)[11,12] and conditional authorization in Europe (August 2021)[13] and other countries for treatment of adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, and who are ineligible for ASCT, and is a preferred treatment option in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) in this setting[1]
 - The current approved dose for tafasitamab is intravenous (IV) infusion of 12 mg/kg once per week during Cycles (C) 1–3 (each C = 28 days), including a loading dose on C1 Day (D) 4, and every 2 weeks (Q2W) thereafter[9,10]
 - Tafasitamab is co-administered with LEN (25 mg/day orally; D1–21 of each cycle) until C12, after which LEN is discontinued and patients receive IV tafasitamab monotherapy Q2W until disease progression or unacceptable toxicity[9,10]
- Longer dosing intervals for IV tafasitamab treatment may allow a reduction in the frequency of hospital/clinical visits and may consequently contribute to improvements in patients' well-being, reduce their exposure to infections during infusion visits, and reduce healthcare utilization

Objective

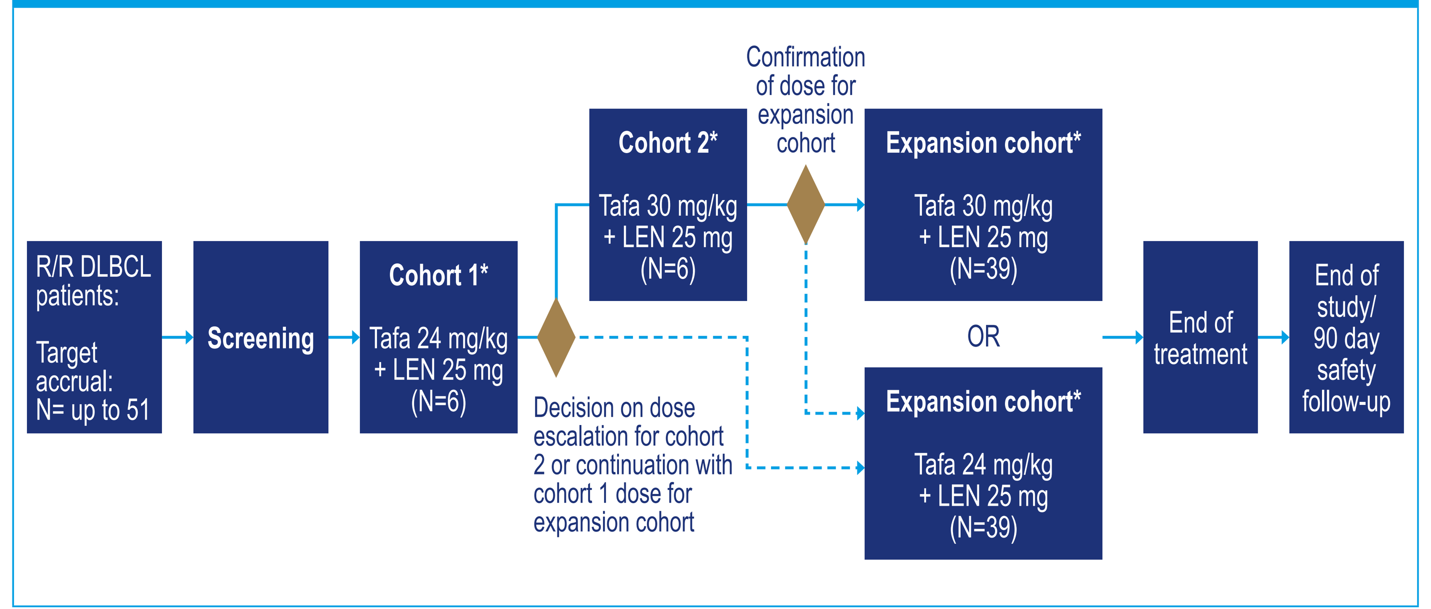
- MINDway (NCT05222555) is a trial in progress, investigating the efficacy and safety of tafasitamab administration at dosages higher than the approved 12 mg/kg dose and at a reduced frequency, and whether the benefit–risk relationship of tafasitamab plus LEN for patients with R/R DLBCL can be maintained

Methods

Study design

- MINDway is an ongoing, open-label, multicenter, Phase Ib/II study, which is currently open for enrollment
- The study will enroll approximately 51 patients with a histologically confirmed diagnosis of R/R DLBCL
- Patients will receive tafasitamab plus LEN in 28-day cycles
- The modified tafasitamab dosing regimen will be investigated in a stepwise design with two sequential dose-finding cohorts (planned n=6 each), followed by an expansion cohort (planned n=39) (Figure 1)

Figure 1. Study design


R/R DLBCL patients:
Target accrual: N= up to 51
Screening
Cohort 1*
Tafa 24 mg/kg + LEN 25 mg (N=6)
Cohort 2*
Tafa 30 mg/kg + LEN 25 mg (N=6)
Confirmation of dose for expansion cohort
Decision on dose escalation for cohort 2 or continuation with cohort 1 dose for expansion cohort
Expansion cohort*
Tafa 30 mg/kg + LEN 25 mg (N=39)
OR
Expansion cohort*
Tafa 24 mg/kg + LEN 25 mg (N=39)
End of treatment
End of study/ 90 day safety follow-up

*In the first 28-day cycle (Cycle 1), tafasitamab is given on D1, D4, and D8 at a dose of 12 mg/kg.
♦ DSMC meeting.
D, Day; DLBCL, diffuse large B-cell lymphoma; DSMC, Data and Safety Monitoring Committee; LEN, lenalidomide; R/R, relapsed/refractory; Tafa, tafasitamab.

Eligibility criteria

- Eligible patients aged 18–80 years with histologically confirmed R/R DLBCL with 1–3 prior systemic regimens, including CD20-targeted therapy, and Eastern Cooperative Oncology Group performance status 0–2 (Table 1)
- Patients previously treated with CD19-targeted therapy, prior ASCT, or immunomodulatory imide drugs, such as LEN, are excluded

Table 1. Key eligibility criteria

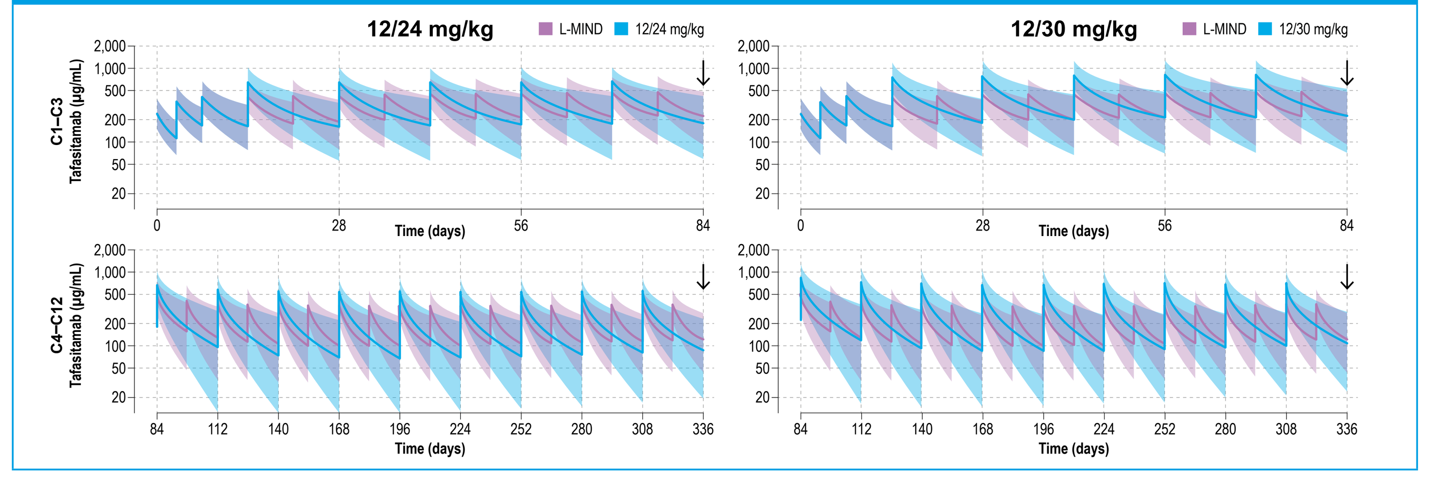
Key inclusion criteria	Key exclusion criteria
• Age 18–80 years • Histologically confirmed R/R DLBCL • 1–3 prior systemic regimens, including CD20-targeted therapy • ECOG PS 0–2 • ≥1 bi-dimensionally measurable disease site • Ineligible for ASCT • Laboratory criteria at screening: – ANC ≥1.5 × 10^9/L – Platelet count ≥75 × 10^9/L – Total serum bilirubin ≤2.5 × ULN unless secondary to Gilbert's syndrome or liver involvement – ALT, AST, and ALP ≤3 × ULN or <5 × ULN in cases of documented liver involvement – Serum creatinine CL ≥50 mL/minute	• Any other histological type of lymphoma • Primary refractory DLBCL • Known 'double/triple hit' genetics (high-grade B-cell lymphoma) • Concomitant CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy, or other lymphoma-specific therapy • Previously treated with CD19-targeted therapy or immunomodulatory imide drugs (e.g. thalidomide, LEN) • Prior allogeneic stem cell transplantation • History of other malignancies, positive hepatitis B and/or C serology, known seropositivity for or history of active HIV infection, present or past medical history of CNS lymphoma involvement • Pregnancy

ANC, absolute neutrophil count; ALP, alkaline phosphatase; ALT, alanine transaminase; ASCT, autologous stem cell transplant; AST, aspartate transaminase; CL, clearance; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; LEN, lenalidomide; R/R, relapsed/refractory; ULN, upper limit of the normal range.

Dose determination using pharmacokinetic (PK) modeling and simulations

- Previous studies have shown that tafasitamab administration according to the recommended dosing regimen reached and maintained a therapeutic dose level in the first-line[12] and second-line[13,14] setting
- A population-PK-based modeling and simulation approach was used to identify alternative dosing regimens, allowing the tafasitamab dosing frequency to be reduced by 50% from C1 D15 onwards while maintaining similar C_{trough} levels, as observed in the pivotal Phase II L-MIND trial[9]
- Initial dosing at 12 mg/kg on C1 D1, D4, and D8 is maintained to reduce the risk of infusion-related reactions
- Model predictions of tafasitamab concentrations at 12/24 mg/kg and 12/30 mg/kg dosing regimen (Table 2) versus L-MIND demonstrate that a tafasitamab dose of 30 mg/kg is required to achieve median C_{trough} levels as previously observed in L-MIND at the end of C3 and C12 (Figure 2), thus maintaining the established exposure/efficacy relationship
- Tafasitamab concentrations for the 12/24 mg/kg and 12/30 mg/kg dosing regimens will exceed maximal levels observed in L-MIND (Figure 2)
- To enable a stepwise evaluation of safety of increased maximal tafasitamab levels, patient enrollment will start in Cohort 1 at 12/24 mg/kg, followed by the targeted 12/30 mg/kg dosing in Cohort 2

Figure 2. Overlay of the model-predicted concentration–time profiles of tafasitamab for L-MIND and the MINDway 12/24 mg/kg and 12/30 mg/kg dosing regimens


12/24 mg/kg
L-MIND
12/24 mg/kg
12/30 mg/kg
L-MIND
12/30 mg/kg
C1–C3 Tafasitamab (µg/mL)
C4–C12 Tafasitamab (µg/mL)
2,000
1,000
500
200
100
50
20
0
28
56
84
112
140
168
196
224
252
280
308
336
Time (days)

Model-predicted tafasitamab serum concentration (µg/mL) over time in 2,000 virtual patients randomly generated using the tafasitamab Pop-PK model. Results are displayed in purple for L-MIND and in blue for the 12/24 mg/kg dosing regimen (left panels) and 12/30 mg/kg dosing regimen (right panels). Data from C1 to C3 are depicted in the upper panels, data from C4 to C12 in the lower panels. Continuous lines represent median of simulated concentration–time profiles, colored area represent the range between the 2.5th and the 97.5th percentiles of the simulated concentration–time profiles. Arrows indicate tafasitamab C_{trough} levels at end of C3 (upper panels) and at end of C12 (lower panels).
C, Cycle; pop-PK, population pharmacokinetics.

MINDway dosing regimens

- Tafasitamab dose (12 mg/kg) will be maintained for the first three infusions (C1 D1, D4, and D8); the dose will be increased from C1 D15 onwards (Table 2)
- Tafasitamab dosing frequency will be reduced from once per week to Q2W from C1 D15 onwards, and from Q2W to every 4 weeks (Q4W) from C4 D1 onwards
- No intra-patient dose escalation from 24 mg/kg to 30 mg/kg will be permitted

Table 2. Dosing regimens assessed during MINDway

Study drug	Cycle	Approved dosing regimen		MINDway Cohort 1		MINDway Cohort 2		MINDway expansion cohort	
Tafasitamab	1	D1, 4, 8, 15, 22	12 mg/kg	D1, 4, 8	12 mg/kg	D1, 4, 8	12 mg/kg	D1, 4, 8	12 mg/kg
				D15	24 mg/kg	D15	30 mg/kg	D15	24 or 30 mg/kg
	2–3	D1, 8, 15, 22	12 mg/kg	D1, 15	24 mg/kg	D1, 15	30 mg/kg	D1, 15	24 or 30 mg/kg
	4+	D1, 15	12 mg/kg	D1	24 mg/kg	D1	30 mg/kg	D1	24 or 30 mg/kg
LEN	1–12	D1–21	25 mg	D1–21	25 mg	D1–21	25 mg	D1–21	25 mg

D, day; LEN, lenalidomide.

Table 4. Key study assessments

Assessments	Screening period	Treatment period (Cycle = 28 days)												Follow-up period
	Screening ≤28 days prior to D1	C1				C2		C3		C4–12	C12	C13 onwards	EOT visit*	90-day safety follow-up/EOS visit†
Day	Screen	D1	D4 ±1 day	D8 ±1 day	D15 ±1 day	D1 ±1 day	D15 ±1 day	D1 ±1 day	D15 ±1 day	D1 ±2 days	D28 ±2 days	D1 ±2 days	Within 14 days after decision on treatment discontinuation	±7 days
Safety and tolerability														
Adverse events (AEs, SAEs, and AESIs)	X	X	X	X	X	X	X	X	X	X		X	X	X
PK and incidence of ADA														
PK tafasitamab		X	X	X	X	X	X	X	X	X	X	X*		
Tafasitamab ADA		X				X		X		X	X		X*	
Imaging, tumor evaluation, and biopsy/tissue														
PET-CT or PET-MRI	X										X‡	X‡	X‡	
CT or MRI								X		X		X		
Bone marrow aspiration and biopsy	X§								X§	X§	X§	X§		
Biomarker assessments														
B-, T-, and NK cell flow cytometry (blood)		X			X	X				C5 D1, C9 D1	X			
MRD by ctDNA analysis (blood)		X				X		X		C5 D1, C7 D1	X	C18 D1, C24 D1		

*EOT samples for PK and ADA will not be collected for patients receiving tafasitamab treatment beyond C12. †Regardless of the reason for treatment discontinuation, patients will have a safety follow-up visit or phone call scheduled 90 days after the last dose of the study treatment. ‡PET-CT or PET-MRI should be performed at screening, at C12 D28 (± 4 days), and at EOT visit unless disease progression was already radiologically confirmed prior to the EOT visit. If progression/relapse is suspected on the basis of clinical symptoms, PET-CT or PET-MRI should be performed to confirm disease progression. PET/CT or PET-MRI from C25 onwards should be performed only if deemed necessary, and not ≥1 per year. §Repeat bone marrow biopsy only in those patients who had known bone marrow involvement at screening to confirm a CR. If repeat bone marrow biopsy is required to confirm CR, the assessment should be done at C3 D15 ± 1 day and/or within 15 days after C5 D1, C7 D1, C10 D1, and C12 D28. Bone marrow assessment from Cycle 13 to 24 approximately every 3 months ± 2 weeks from the previous assessment to be performed to confirm a CR only in those patients who had known marrow involvement at screening.
AE, adverse event; ADA, anti-drug antibodies; AESI, adverse event of special interest; C, cycle; CR, complete response; CT, computed tomography; ctDNA, circulating tumor DNA; D, day; EOS, end of study; EOT, end of treatment; MRD, minimal residual disease; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; SAE, serious adverse event.

- Tafasitamab plus LEN will be administered until disease progression, unacceptable toxicity, or discontinuation due to other reason, whichever comes first
- The end of the study is the date when the last patient completes their last visit

Study endpoints

- The primary endpoint is evaluation of the safety and tolerability of a modified tafasitamab dosing regimen in patients with R/R DLBCL (Table 3)
- All clinical efficacy endpoints will be assessed according to the revised response criteria for malignant lymphoma based on The International Working Group Resource Criteria[15]
- All endpoints will be analyzed using descriptive statistics; no formal statistical tests will be performed
- Histologic examination and imaging assessments of efficacy and disease response will be recorded, during the course of the study, and safety assessments will be monitored continuously to ensure patient safety (Table 4)

Table 3. Study objectives and corresponding endpoints

Objectives	Study endpoints
Primary	
• Safety and tolerability of tafasitamab administered Q2W/Q4W in combination with LEN • Recommended dose for tafasitamab Q2W/Q4W administration in combination with LEN	• Incidence and severity of TEAEs
Secondary	
• Pharmacokinetic profile of tafasitamab after Q2W/Q4W dosing in combination with LEN	• Tafasitamab serum concentrations after C3 (C_{trough} and C_{max}) and C12 (C_{trough})
• Anti-tumor activity of tafasitamab after Q2W/Q4W dosing in combination with LEN	• Best ORR up to C12 as assessed by the investigator • DoR as assessed by the investigator • PFS as assessed by the investigator
• Incidence of anti-drug antibodies to tafasitamab	• Number and percentage of patients developing anti-tafasitamab antibodies up to C12*
Exploratory	
• Longitudinal analysis of B-, T-, and NK cell numbers in peripheral blood	• Absolute counts and percentage change from baseline in measurements of B-, T-, and NK cell numbers in peripheral blood
• MRD burden and tumor mutational signature by serial ctDNA assessment	• ctDNA levels and mutational profile, and MRD status by visit

*Each treatment cycle is 28 days.
C, cycle; C_{max}, maximum concentration; ctDNA, circulating tumor DNA; C_{trough}, minimum concentration; DoR, duration of response; LEN, lenalidomide; MRD, minimal residual disease; NK, natural killer; ORR, objective response rate; PFS, progression-free survival; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TEAEs, treatment-emergent adverse events.

Summary

- The MINDway study will investigate the efficacy and safety of tafasitamab plus LEN, and tafasitamab PK, in a modified tafasitamab dosing regimen in patients with R/R DLBCL
 - The tafasitamab dosing frequency will be reduced from once per week to Q2W from C1 D15 onwards, and then from Q2W to Q4W from C4 D1 onwards
- A reduced frequency of hospital/clinic visits may improve patient convenience and support long-term treatment adherence
- MINDway is open for enrollment

Acknowledgments

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Disclosures

About Tafasitamab
Tafasitamab is a humanized Fc-modified cytolytic CD19-targeting monoclonal antibody. In 2010, MorphoSys licensed exclusive worldwide rights to develop and commercialize tafasitamab from Xencor, Inc. Tafasitamab incorporates an XmAb® engineered Fc domain, which mediates B-cell lysis through apoptosis and immune effector mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). In January 2020, MorphoSys and Incyte entered into a collaboration and licensing agreement to further develop and commercialize tafasitamab globally. Following approval by the U.S. Food and Drug Administration in July 2020, tafasitamab is being co-commercialized by MorphoSys and Incyte in the United States. Conditional/accelerated approvals were granted by the European Medicines Agency and other regulatory authorities. Incyte has exclusive commercialization rights outside the United States. XmAb® is a registered trademark of Xencor, Inc.

Conflicts of interest
RG: honoraria: Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, BMS, MSD, Sandoz, AbbVie, Gilead Sciences, Daiichi Sankyo, Sanofi; consultancy: Celgene, Novartis, Roche, BMS, Takeda, AbbVie, AstraZeneca, Janssen, MSD, Merck, Gilead Sciences, Daiichi Sankyo, Sanofi; research funding: Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, BMS, MSD, Sandoz, AbbVie, Gilead Sciences, Daiichi Sankyo. **KK:** stock: Viatris; consultancy: Pierre Fabre; travel expenses: Bayer. **LA:** consulting/advisory: Roche, Janssen-Cilag, Verastem, Incyte, EUSA Pharma, Celgene/BMS, Gilead Sciences/Kite, ADC Therapeutics; speakers' bureau: EUSA Pharma, Novartis; travel, accommodation, expenses: Roche, Celgene, Janssen-Cilag, EUSA Pharma; research funding: Gilead Sciences. **AA:** employment: MorphoSys AG; stock: Paion AG; **KG:** employment: MorphoSys AG. **CT:** employment: MorphoSys AG.

References

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2. Coiffier B, Sarkozy C. Hematol Am Soc Hematol Educ Progr 2016;2016(1):366–78.
3. Sarkozy C, Sehn LH. Ann Lymphoma 2019;310.
4. Crump M, et al. Blood 2017;130(16):1800–8.
5. Sarkozy C, Coiffier B. Clin Cancer Res 2013;19(7):1660–9.
6. González-Barca E, et al. Bone Marrow Transplant 2020;55:393–9.
7. Gisselbrecht C, et al. J Clin Oncol 2010;28(27):4184–90.
8. Chihara D, et al. Biol Blood Marrow Transplant 2014;20(5):684–9.
9. Salles G, et al. Lancet Oncol 2020;21(7):978–88.
10. Duell J, et al. Haematologica 2021;106(9):2417–26.
11. MONJUVI. Prescribing information. Boston, MA: MorphoSys. 2020. https://www.monjuvi.com/pi/monjuvi-pi.pdf [Accessed July 2022].
12. Belada D, et al. J Clin Oncol 2022:e19553.
13. European Medicines Agency. Minjuvi. https://www.ema.europa.eu/en/medicines/human/EPAR/minjuvi [Accessed July 2022].
14. Jurczak W, et al. Ann Oncol 2018;29(5):1266–72.
15. Cheson BD, et al. J Clin Oncol 2007;25(5):579–86.

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