Summary Report of Benefit-Risk Assessment

IMDELLTRA POWDER FOR SOLUTION FOR INFUSION 1 MG/VIAL
IMDELLTRA POWDER FOR SOLUTION FOR INFUSION 10 MG/VIAL

NEW DRUG APPLICATION

Active Ingredient	Tarlatamab
Product Registrant	Amgen Biotechnology Singapore Pte Ltd
Product Registration Numbers	SIN17299P, SIN17300P
Application Route	Abridged evaluation
Date of Approval	01 August 2025

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A INTRODUCTION

Imdelltra is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

The active substance, tarlatamab, is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager. The DLL3 protein is found in 85% to 96% of SCLC cases and is rarely found in healthy cells. Tarlatamab causes T-cell activation, production of inflammatory cytokines and release of cytotoxic proteins which results in the lysis of DLL3-expressing cells.

Imdelltra is available as a sterile, preservative-free, white to slightly yellow, lyophilised powder supplied in a single-dose vial containing 1 mg or 10 mg of tarlatamab co-packaged with 2 vials of IV solution stabiliser to coat the intravenous bag prior to addition of the reconstituted solution for infusion to prevent adsorption of tarlatamab to the IV bags and IV tubing.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, tarlatamab, is manufactured at Immunex Rhode Island Corporation, Rhode Island, USA. The drug product, Imdelltra powder for solution for infusion, is manufactured at Amgen Inc, California, USA. The IV solution stabiliser is manufactured at Amgen Technology (Ireland) Unlimited Company, Dun Laoghaire, Ireland.

Drug substance

Adequate controls have been presented for the reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP) standard. Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the manufacturing process and specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline, and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at -30°C with a shelf life of 36 months. The packaging is single-use, triple layer-film bag with an ethylene-vinyl acetate (EVA) product contact layer.

Drug product (powder)

The manufacturing process involves formulation of the drug product, followed by prefiltration, sterile filtration, aseptic filling and lyophilisation. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored between 2°C and 8°C. The container closure system is a Type I glass vial with an elastomeric stopper with fluoropolymer film laminated on product contact surface and an aluminium seal with flip-off cap.

Drug product (IV solution stabiliser)

The IV solution stabiliser comprises citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide, and water for injection, all of which meet pharmacopoeial grade standards. The manufacturing process involves formulation followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B guideline. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines.

The stability data submitted was adequate to support the approved shelf-life of 60 months when stored at 2°C and 8°C. The container closure system is a Type I glass vial with an elastomeric stopper with fluoropolymer film laminated on product contact surface and an aluminium seal with flip-off cap.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of tarlatamab was based on one Phase II study, Study DeLLphi-301 and supported by the topline results of the Phase III study, Study DeLLphi-304.

Study DeLLphi-301 was an open-label, multicentre, multicohort study in patients with relapsed or refractory ES-SCLC with disease progression on or after platinum-based chemotherapy and at least one other line of prior therapy (third-line and beyond setting), and had an ECOG Performance Status of 0 or 1 and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Patients with symptomatic brain metastases, evidence of interstitial lung disease or non-infectious pneumonitis, and active immunodeficiency were excluded.

The study consisted of three parts. In all three parts, patients received a step dose of 1 mg of tarlatamab on Day 1 of Cycle 1, after which they received the target dose of either 10 mg or

100 mg on Day 8 and Day 15 of Cycle 1 and every 2 weeks thereafter in 28-day cycles (two doses per cycle) until disease progression or unacceptable toxicity. An 8 mg dose of dexamethasone was administered intravenously before tarlatamab was given on Day 1 and Day 8 of Cycle 1. Prophylactic hydration with normal saline was administered intravenously after each dose in Cycle 1.

Part 1 involved a dose-comparison assessment in approximately 180 patients who were randomised in a 1:1 ratio to receive 10 mg of tarlatamab or 100 mg of tarlatamab intravenously during a 60-minute infusion. A prespecified interim analysis was performed after 30 patients per group were evaluated for objective response after the first post-treatment scan, or had been followed for 13 weeks, whichever came first. Based on the review of an independent dose-selection committee, the selected dose for Parts 2 and 3 of the trial was determined to be 10 mg on Day 8 and Day 15 of Cycle 1 and every 2 weeks thereafter.

In Part 2, patients were enrolled until approximately 100 patients (from Parts 1 and 2 combined) had been enrolled at that selected dose. For Parts 1 and 2, patients were hospitalised for safety monitoring for 48 hours post tarlatamab infusion for Cycle 1 Day 1 and Day 8 doses.

Part 3 was a substudy performed after the enrolment of patients in Part 2 was completed and enrolled approximately 30 additional subjects at the selected dose with a reduced inpatient monitoring from 48 to 24 hours after the infusion during Cycle 1.

Imaging assessments were scheduled every 6 weeks for the first 48 weeks, then every 12 weeks thereafter. Treatment could be allowed to continue after radiographic progression if the investigator judged that tarlatamab remained clinically beneficial to the patient. Safety follow-up occurred 6 weeks after the last dose of tarlatamab, and long-term follow-up visits occurred every 3 months for 1 year after the last patient's last dose of tarlatamab or every 3 months for 5 years after the first patient was enrolled, whichever occurred first.

The primary efficacy endpoint was overall response rate (ORR) as evaluated by the blinded independent central review (Parts 1 and 2) according to RECIST v1.1. Duration of response (DoR) was the key secondary endpoint.

Time-to-event endpoints of progression-free survival (PFS) and overall survival (OS) were not interpretable in the absence of an appropriate control arm.

A total of 222 patients were randomised (Part 1) or enrolled (Parts 2 and 3), and 220 patients received at least 1 dose of tarlatamab. These patients were distributed across three groups: 99 patients received 10 mg (Part 1 and Part 2), 87 patients received 100 mg (Part 1 only), and 34 patients received 10 mg under modified safety monitoring (Part 3). The 100 mg dose was not selected for further investigation in Parts 2 and 3 of the trial due to lower efficacy compared to the 10 mg dose (ORR 33% vs 41%) and increased toxicities. Hence, the efficacy analysis focused on the 99 patients who received the recommended dose of 10 mg in Parts 1 and 2 of the study.

The median age was 64 years (range 35 to 82). A total of 72% were male, 58% were White and 41% were Asians. The majority had metastatic disease at baseline (97%) and 22% had asymptomatic brain metastases. All patients received prior platinum-based chemotherapy (median of two lines); 74% received prior anti-PD-(L)1 therapy (including 59% who received anti-PD[L]1 therapy in combination with platinum-based chemotherapy in the frontline setting); and 51% received prior topoisomerase I inhibitor (including 20% who received topotecan). Platinum sensitivity status, defined by time to progression after first line platinum therapy, was

known for 69 of 99 patients. A total of 27% had platinum-resistant ES-SCLC, defined as time to progression <90 days after first-line platinum therapy, while 42% had platinum-sensitive ES-SCLC.

At the updated efficacy analysis data cut-off date (DCO) of 12 January 2024, a total of 40 patients in Parts 1 and 2 had a response in the 10 mg dose group, and the ORR was 40% (95% confidence interval [CI]: 31, 51). The observed ORR of 40% was considered promising over available therapies in a heavily pre-treated population. The observed ORR was generally consistent across most patient subgroups, defined by relevant demographic and disease-related characteristics, including across subgroups of patients with platinum-sensitive and platinum-refractory disease and across subgroups with various DLL3 expression cut-offs.

In the subgroup analyses stratified by platinum-resistant and -sensitive status, the ORR was 52% (95% CI: 32%, 71%) in 27 patients with platinum-resistant ES-SCLC (defined as <90 days after the end of first-line platinum therapy to date of progression) and 31% (95% CI: 18%, 47%) in 42 patients with platinum-sensitive ES-SCLC (defined as ≥90 days after end of first-line platinum therapy to date of progression). The 95% CIs overlapped, which suggests that a true difference in efficacy based on platinum sensitivity status was unlikely considering the mechanism of action of tarlatamab as a targeted agent that causes activation of the immune system.

The observed ORR was supported by a durable median DoR of 9.7 months with a median follow-up time of 15.1 months. There were 68% of patients with an observed DoR ≥6 months and 40% of patients with an observed DoR ≥12 months.

Efficacy results of DeLLphi-301 (Parts 1 and 2) – Data cut-off 12 January 2024

	1 → 10mg (N=99)
Best overall response – n (%)	
Confirmed complete response	2 (2)
Confirmed partial response	38 (38)
Confirmed ORR – % (95% CI)	40% (31, 51)
DoR (months)	n=40
Median (95% CI)	9.7 (6.9, NE)
Range	2.7, 20.7+
Duration ≥ 6 months	68%
Duration ≥ 9 months	50%
Duration ≥ 12 months	40%
Median follow-up time	15.1

NE: not estimable

Overall, the efficacy results were promising in patients with relapsed or refractory ES-SCLC who have limited treatment options and for whom there is a high unmet need for effective treatment options.

These results were further supplemented by the topline data from Study DeLLphi-304, which was an ongoing, Phase III, open-label, randomised, multicentre confirmatory study evaluating the efficacy and safety of tarlatamab compared with the standard-of-care (SOC) for the treatment of subjects with ES-SCLC who have progressed on or after platinum-based chemotherapy (second-line and beyond setting).

In Study DeLLphi-304, patients were randomised in a 1:1 ratio to receive tarlatamab or SOC chemotherapy (lurbinectedin or topotecan in the USA, Canada, Australia, Singapore, Korea; amrubicin in Japan; topotecan in all countries except Japan).

The primary efficacy endpoint of the study was OS, defined as time from randomisation until death from any cause. Secondary endpoints included PFS, ORR and DoR based on investigator assessment per RECIST v1.1.

A total of 254 patients were randomised to receive tarlatamab 10 mg and 255 patients randomised to receive SOC chemotherapy (208 amrubicin/topotecan and 47 lurbinectedin). Subjects received study treatment until investigator-determined radiographic disease progression per RECIST 1.1, unacceptable toxicity, withdrawal of consent, death, or end of study as determined by the sponsor.

Baseline demographics and disease characteristics were generally balanced across the groups. The median age of the subjects was 65.0 years (range: 20 to 86) and 69.0% were male. Overall, 57.2% of subjects were White and 40.1% were Asian.

The majority of patients (67.2%) had an ECOG performance status of 1; 44.8% had brain metastases (previous or current) at baseline; 35.2% had liver metastases at baseline; 70.7% received prior PD-(L)1 inhibitor therapy; 43.8% were platinum-resistant (defined as chemotherapy-free interval (CFI) <90 days after first-line platinum therapy), and 56.2% were platinum-sensitive (defined as CFI ≥90 days). Almost all patients had received one prior line of therapy (97.6%) and 2.4% received ≥2 prior lines.

Based on the topline results, a total of 263 deaths and 396 PFS events were reached at the primary analysis for OS (DCO of 29 January 2025). Tarlatamab demonstrated a statistically significant and clinically meaningful OS benefit (median OS 13.6 months vs 8.3 months, hazard ratio [HR] 0.599 [95% CI: 0.468, 0.768], p<0.001) with a 40.1% reduced risk of death compared with SOC. A modest benefit for the key secondary endpoint of PFS was demonstrated with tarlatamab as compared with SOC, with a median PFS of 4.2 months vs 3.2 months (HR 0.716 [95% CI: 0.586, 0.875], p<0.001). The ORR of 35.0% was consistent with that observed in the Phase II DeLLphi-301 study and was higher as compared to SOC (20.4%). The median DoR was 6.9 months in the tarlatamab group vs 5.5 months in the SOC group.

Overall, Study DeLLphi-301 provided evidence of treatment benefit for tarlatamab in terms of a clinically meaningful ORR of 40% (95% CI 31, 51). Despite the limitations of being a single-arm Phase II study, the results observed in heavily pre-treated relapsed or refractory ES-SCLC patients who had progressed on or after platinum-based chemotherapy and at least one other line of prior therapy, demonstrated clinically meaningful improvements when compared against the current standard of care, topotecan, where ORR ranged between 7.6% to 24.3%. The observed efficacy was also supported by a durable median DoR of 9.7 months. The evidence from Study DeLLphi-301 was further supplemented by topline results from the ongoing Phase III confirmatory active-comparator Study DeLLphi-304 where a statistically significant and clinically meaningful OS benefit of 5.3 months with tarlatamab as compared to standard of care was observed. The final study report of Study DeLLphi-304 will be required to be submitted to confirm the clinical benefit of tarlatamab for the target patient population.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of tarlatamab was based primarily on the pooled safety data derived from the pivotal Phase II Study DeLLphi-301 and the first-in-human Phase I study. As of the DCO of 02 October 2023, a total of 187 patients with ES-SCLC received the dosage of 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8 and 15, and then every 2 weeks until disease progression or intolerable toxicity. A total of 31% of patients had a treatment exposure of 6 months or longer, and 14% had a treatment exposure for more than one year.

Overview of safety profile (DCO 02 October 2023)

Adverse Event (AE)	Tarlatamab 1 → 10 mg (N=187) n (%)
Any AE	186 (99.5)
Treatment-related AE	175 (93.6)
Serious AE (SAE)	104 (55.6)
Treatment-related SAE	62 (33.2)
Discontinuations due to AE	13 (7.0)
Deaths due to AE	7 (3.7)

Treatment-emergent AEs were reported in almost all subjects (99.5%) who received at least 1 dose of tarlatamab at the recommended dosing regimen, with 93.6% experiencing treatment-related AEs. The majority of the treatment-related AEs were of Grade 2 or less in severity. Grade ≥3 treatment-related AEs were reported in 33.7% of subjects. The most common (>20%) treatment-emergent AEs were cytokine release syndrome [CRS] (55%), fatigue (51%), dysgeusia (36%), pyrexia (36%), decreased appetite (34%), constipation (30%), musculoskeletal pain (30%), anaemia (27%) and nausea (22%).

SAEs were reported for 104 subjects (55.6%), and 33.2% of subjects reported treatment-related SAEs. The most frequently reported SAEs included CRS (23.5%), pneumonia (3.7%) and pyrexia (3.7%).

AEs leading to tarlatamab treatment discontinuation occurred in 7.0% of subjects, and 3.2% of subjects reported AEs leading to treatment discontinuations that were deemed related to tarlatamab. The most frequently reported AEs leading to treatment discontinuations were CRS and tumour lysis syndrome (1.1% each).

Fatal AEs were reported in 7 (3.7%) subjects, with 1 event (respiratory failure) considered as related to treatment.

The key AEs of special interest with tarlatamab were CRS and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS). In the pooled safety population, CRS occurred in 55% of patients treated with tarlatamab, including 34% Grade 1, 19% Grade 2, 1.1% Grade 3 and 0.5% Grade 4. Recurrent CRS occurred in 24% of tarlatamab-treated patients (18% Grade 1 and 6% Grade 2). Among patients who experienced CRS, the majority had onset after the first dose (43%), followed by 29% after the second dose and 9% following the third dose or later. The incidence of Grade ≥2 CRS showed progressive reduction with successive infusions, occurring in 16% of patients after Day 1, 4.3% after Day 8, and 2.1% after Day 15 dosing. The median time to onset of all grade CRS from most recent dose of tarlatamab was 13.5 hours (range: 1 to 268 hours). The median time to onset of ≥Grade 2 CRS from most recent dose of tarlatamab was 14.6 hours (range: 2 to 566 hours).

Neurologic toxicities occurred in 47% of patients in the pooled safety population, of which 10% were of Grade 3 severity. No Grade 4 events were reported. These toxicities included ICANS. The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%), insomnia (6%), muscular weakness (3.7%), delirium (2.1%), syncope (1.6%) and neurotoxicity (1.1%). ICANS occurred in 9% of patients and recurrent ICANS occurred in 1.6% of patients. Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5% and 3.7% of patients experienced Grade ≥2 ICANS, respectively. Most patients experienced ICANS following Cycle 2 Day 1 (24%). The median time to onset of ICANS from the first dose of tarlatamab was 29.5 days (range: 1 to 154 days). The median time to resolution of ICANS was 33 days (range: 1 to 93 days). Per the study protocol, patients were hospitalised for 48 hours post-tarlatamab infusion for the Cycle 1 Day 1 and Cycle 1 Day 8 doses, except for patients in Part 3 of Study DeLLphi-301, who were hospitalised for 24 hours post-tarlatamab infusion for Cycle 1 Day 1 and Cycle 1 Day 8 doses.

Based on the review of currently available safety data, monitoring of patients for 22 to 24 hours following Cycle 1 Day 1 and Cycle 1 Day 8 administration in an appropriate healthcare setting was deemed reasonable to mitigate the safety risks of CRS and ICANS.

The safety profile of tarlatamab remained consistent with the updated safety data cut-off date of 18 October 2024.

Overall, tarlatamab treatment was associated with significant toxicities, which was not unexpected considering the mechanism of action. The potential safety risks of CRS and ICANS require mitigation through pre-medications, step-up dosing schedule with monitoring post-infusion, dose interruptions and modifications. These risk mitigation measures have been included in the product labelling. In addition, patients will be provided with a Patient Alert Card to ensure they receive the necessary advice and information on the safety risks associated with tarlatamab treatment. In the context of a life-threatening disease with a poor prognosis and limited treatment options, these toxicities are considered acceptable.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Extensive stage small cell lung cancer has poor prognosis and limited treatment options after progression on first-line chemotherapy or in combination with immunotherapy. Currently approved second-line treatments include lurbinectedin and topotecan. Given the limited efficacy of existing therapies for resistant disease, there is an unmet medical need for new treatment options for these patients.

Study DeLLphi-301 presented reasonable evidence supporting the use of tarlatamab monotherapy in a heavily pre-treated ES-SCLC population with a clinically meaningful ORR of 40% and a durable median DOR of 9.7 months. Notably, the observed ORR of 52% in patients with platinum-resistant disease with tarlatamab represented a significant improvement in the context of a life-threatening disease characterised by short survival and low response to subsequent therapies.

In the on-going Phase III study, Study DeLLphi-304, the topline results were reassuring that a statistically significant and clinically relevant improvement of 5.3 months in survival benefit was observed with tarlatamab as compared to standard of care.

While the improvement in PFS with tarlatamab was modest with a 1-month PFS benefit over SOC, the observed ORR of 35% in the second-line setting was consistent with the ORR observed in the third-line setting in the DeLLphi-301 study.

Overall, the safety profile of tarlatamab showed significant toxicities. The most notable safety concerns with tarlatamab were CRS and neurologic toxicity including ICANS, of which the majority were of Grades 1 to 2 in severity. The relevant warnings and precautions, as well as recommendations for monitoring and dose interruption or discontinuation have been adequately described in the package insert. In addition, the Patient Alert Card serves to remind physicians and patients on the signs and symptoms of CRS and ICANS to facilitate early detection and clinical management. The safety profile of tarlatamab was considered acceptable relative to the potential benefits in this heavily pre-treated population with limited treatment options.

Taking the available evidence in totality, the benefit-risk assessment of tarlatamab in the treatment of ES-SCLC post-progression on or after platinum-based chemotherapy was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Imdelltra for the treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy was deemed favourable and approval of the product registration was granted on 01 August 2025. The approval is subject to the submission of the final study report of the Phase III Study DeLLphi-304 to confirm the clinical benefit and demonstrate a favourable overall benefit-risk profile of Imdelltra.

APPROVED PACKAGE INSERT AT REGISTRATION

FULL PRESCRIBING INFORMATION
IMDELLTRA POWDER FOR SOLUTION FOR INFUSION 1 MG/VIAL
IMDELLTRA POWDER FOR SOLUTION FOR INFUSION 10 MG/VIAL

1 INDICATIONS AND USAGE

IMDELLTRA is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

- Administer IMDELLTRA according to the step-up dosing schedule in Table 1 to reduce the incidence and severity of cytokine release syndrome (CRS) *[see Dosage and Administration (2.2)].*
- For Cycle 1, administer recommended concomitant medications in Table 3 before and after Cycle 1 IMDELLTRA infusions to reduce the risk of CRS reactions *[see Dosage and Administration (2.3)].*
- IMDELLTRA should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) *[see Warnings and Precautions (5.1, 5.2)].*
- Due to the risk of CRS and neurologic toxicity, including ICANS, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1, 5.2)].*
- Recommend that patients remain within 1-hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.
- Prior to administration of IMDELLTRA evaluate complete blood count, liver enzymes and bilirubin before each dose, and as clinically indicated *[see Warnings and Precautions (5.3, 5.5)].*
- Ensure patients are well hydrated prior to administration of IMDELLTRA *[see Warnings and Precautions (5.1)].*

2.2 Recommended Dosage and Administration

- Administer IMDELLTRA as an intravenous infusion over one hour.
- The recommended step-up dosage schedule for IMDELLTRA is provided in Table 1. Administer following step-up dosing to reduce the incidence and severity of CRS.
- After step-up dosing schedule, administer IMDELLTRA biweekly (every 2 weeks) until disease progression or unacceptable toxicity.

Table 1. Recommended Dosage and Schedule of IMDELLTRA

Dosing Schedule	Day	Dose of IMDELLTRA	Administration Instructions	Recommended Monitoring
Step-up Dosing Schedule Cycle 1	Day 1[a]	Step-up dose[a] 1 mg	Administer IMDELLTRA as a 1-hour intravenous infusion in an appropriate healthcare setting.	Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting. Recommend that patients remain within 1-hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA, accompanied by a caregiver.
	Day 8[a]	10 mg[a]		
	Day 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion[b].
Cycle 2	Day 1 and 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion[b].
Cycles 3 and 4	Day 1 and 15	10 mg		Observe patients for 3-4 hours post IMDELLTRA infusion [b].
Cycle 5 and subsequent infusions	Day 1 and 15	10 mg		Observe patients for 2 hours post IMDELLTRA infusion [b].

[a] Administer recommended concomitant medications before and after Cycle 1 IMDELLTRA infusions as described in Table 3

[b] Extended monitoring in a healthcare setting is not required unless the patient experiences Grade ≥2 CRS, ICANS or neurological toxicity during prior treatments. See Tables 5 and 6 for monitoring recommendations. Note: see Table 4 for recommendation on restarting IMDELLTRA after dose delays.

Administration

- The intravenous (IV) catheter for concomitant medications administration can be used to administer the IMDELLTRA infusion.
- To ensure patency, flush the IV catheter over 3-5 mins using 0.9% Sodium Chloride for Injection.
- Administer the reconstituted and diluted IMDELLTRA as an intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- Table 2 provides the infusion duration and rate.

Table 2. IMDELLTRA Infusion Duration and Rate

Infusion Duration for 250 mL IV Preparation	Infusion Rate
1-hour	250 mL/hour

2.3 Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1

Administer recommended concomitant medications for IMDELLTRA administration during Cycle 1 as presented in Table 3 to reduce the risk of cytokine release syndrome *[see Warnings and Precautions (5.1)].*

Table 3. Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1

Treatment Day	Medication	Administration
Day 1 and Day 8	Administer 8 mg of dexamethasone intravenously (or equivalent)	Within 1-hour prior to IMDELLTRA administration
Day 1, Day 8 and Day 15	Administer 1 liter of normal saline intravenously over 4-5 hours	Immediately after completion of IMDELLTRA infusion

2.4 Restarting IMDELLTRA After Dosage Delay

If a dose of IMDELLTRA is delayed, restart therapy based on the recommendation as listed in Table 4 and resume the dosing schedule accordingly *[see Dosage and Administration (2.2)].* Administer recommended concomitant medications as indicated in section 2.3.

Table 4. Recommendations for Restarting Therapy with IMDELLTRA After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action[a]

1 mg on Cycle 1 Day 1	2 weeks or less (≤14 days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 2 weeks (>14 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.
10 mg on Cycle 1 Day 8	3 weeks or less (≤21 days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 3 weeks (>21 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.
10 mg on Cycle 1 Day 15 and subsequent Cycles every 2 weeks thereafter	4 weeks or less (≤28 days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 4 weeks (>28 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.

[a] Administer recommended concomitant medications before and after Cycle 1 IMDELLTRA infusions and monitor patients accordingly *[see Dosage and Administration (2.1, 2.2 and 2.3)]*.

2.5 IMDELLTRA Dosage Modifications and Adverse Reaction Management

No dose reduction for IMDELLTRA is recommended. See Table 5 and Table 6 for recommended actions for the management of CRS, neurologic toxicity including ICANS respectively and Table 7 for cytopenias, infections and other adverse reactions.

Cytokine Release Syndrome (CRS)

Diagnose CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension.

If CRS is suspected, manage according to the recommendations in Table 5. Monitor patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygen) with continuous cardiac telemetry and pulse oximetry.

For severe or life-threatening CRS, recommend administering tocilizumab or equivalent therapy and intensive monitoring (e.g., ICU) for supportive therapy. Perform laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

Table 5 provides the guidelines for grading and dosage modification and management of cytokine release syndrome.

Table 5. Guidelines for Grading and Dosage Modification and Management of Cytokine Release Syndrome[a]

CRS Grade	Defining Symptoms	IMDELLTRA Dosage Modification	Management
Grade 1	Symptoms require symptomatic treatment only (e.g., fever ≥ 100.4°F without hypotension or hypoxia).	Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose[b].	• Administer symptomatic treatment (e.g., acetaminophen) for fever.
Grade 2	Symptoms require and respond to moderate intervention. • Fever ≥ 100.4°F, • Hypotension responsive to fluids not requiring vasopressors, and/or • Hypoxia requiring low flow nasal cannula or blow-by.	Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose[b].	• Recommend hospitalization for a minimum of 24 hours with cardiac telemetry and pulse oximetry. • Administer symptomatic treatment (e.g., acetaminophen) for fever. • Administer supplemental oxygen and intravenous fluids when indicated. • Consider dexamethasone[c] (or equivalent) 8 mg IV. • Consider tocilizumab (or equivalent). When resuming treatment at the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours in an appropriate healthcare setting.
Grade 3	Severe symptoms defined as temperature ≥ 38°C with: • Hemodynamic instability requiring a vasopressor (with or without vasopressin) or • Worsening hypoxia or respiratory distress requiring high flow nasal canula (> 6 L/min oxygen) or face mask.	Withhold IMDELLTRA until the event resolves, then resume IMDELLTRA at the next scheduled dose[b]. For recurrent Grade 3 events, permanently discontinue IMDELLTRA.	In addition to Grade 2 treatment: • Recommend intensive monitoring, e.g., ICU care. • Administer dexamethasone[c] (or equivalent) 8 mg IV every 8 hours up to 3 doses. • Vasopressor support as needed. • High flow oxygen support as needed. • Recommend tocilizumab (or equivalent) • Prior to the next dose, administer concomitant medications as recommended for Cycle 1 (see Table 3). When resuming treatment at the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours in an appropriate healthcare setting.

CRS Grade	Defining Symptoms	IMDELLTRA Dosage Modification	Management
Grade 4	Life-threatening symptoms defined as temperature ≥100.4°F with: • Hemodynamic instability requiring multiple vasopressors (excluding vasopressin). • Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure.	Permanently discontinue IMDELLTRA.	• ICU care. • Per Grade 3 treatment. • Recommend tocilizumab (or equivalent).

[a] CRS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).
[b] See Table 4 for recommendations on restarting IMDELLTRA after dose delays *[see Dosage and Administration (2.4)]*
[c] Taper steroids per standard of care guidelines.

Neurologic Toxicity including ICANS

At the first sign of neurologic toxicity, including ICANS, withhold IMDELLTRA and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS *[see Warnings and Precautions (5.2)]*. Manage ICANS and neurologic toxicity according to the recommendations in Table 6 and consider further management per current practice guidelines.

Table 6. Guidelines for Management of Neurologic Toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome[a]

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
Grade 1[a]	ICE score 7-9[b] with no depressed level of consciousness.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].	• Supportive care.
Grade 2[a]	ICE score 3-6[b] and/or mild somnolence awaking to voice.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].	• Supportive care. • Dexamethasone[d] (or equivalent) 10 mg IV. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if symptoms worsen. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Monitor patients for 22 to 24 hours following the next dose of IMDELLTRA.
Grade 3[a]	ICE score 0-2[b] and/or depressed level of consciousness awakening only to tactile stimulus and/or any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention and/or Focal or local edema on neuroimaging.	• Withhold IMDELLTRA until the ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c]. • If there is no improvement to grade ≤ 1 within 7 days or grade 3 toxicity reoccurs within 7 days of reinitiation, permanently discontinue IMDELLTRA. • For recurrent grade 3 events, permanently discontinue.	• Recommend intensive monitoring, e.g., ICU care. • Consider mechanical ventilation for airway protection. Dexamethasone[d] (or equivalent) 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Monitor patients for 22 to 24 hours following the next dose of IMDELLTRA.
Grade 4[a]	ICE score 0[b] (patient is unarousable and unable to perform ICE) and/or Stupor or coma and/or Life-threatening prolonged seizure (>	• Permanently discontinue IMDELLTRA.	• ICU care. • Consider mechanical ventilation for airway protection. • High dose corticosteroids[d].

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
	5 minutes) or repetitive clinical or electrical seizures without return to baseline in between and/or diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing's triad.		• Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

[a] ICANS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019)

[b] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (names 3 objects, e.g., point to clock, pen, button = 3 points); Following commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[c] See Table 4 for recommendations on restarting IMDELLTRA after dose delays *[see Dosage and Administration (2.4)]*

[d] Taper steroids per standard of care guidelines

Table 7. Recommended Treatment Interruptions of IMDELLTRA for the Management of Cytopenias, Infections, and Other Adverse Reactions

Adverse Reactions	Severity[b]	Dosage Modification[a]
Cytopenias *[see Warnings and Precautions (5.3)]*	Grade 3 or Grade 4 Neutropenia	Withhold IMDELLTRA until recovery to ≤Grade 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if recovery to ≤Grade 2 does not occur within 3 weeks.
	Recurrent Grade 4 Neutropenia	Permanently discontinue IMDELLTRA
	Febrile neutropenia	Withhold IMDELLTRA until neutropenia recovers to ≤Grade 2 and fever resolves.
	Hemoglobin <8 g/dL	Withhold IMDELLTRA until hemoglobin is ≥8 g/dL.
	Grade 3 or Grade 4 Decreased platelet count	Withhold IMDELLTRA until platelet count is ≤Grade 2 and no evidence of bleeding. Permanently discontinue if recovery to ≤Grade 2 does not occur within 3 weeks.
	Recurrent Grade 4 Decreased platelet count	Permanently discontinue IMDELLTRA.
Infections *[see Warnings and Precautions (5.4)]*	All Grades	Withhold IMDELLTRA in the step-up phase in patients until infection resolves.
	Grade 3	Withhold IMDELLTRA during the treatment phase until infection improves to ≤Grade 1[a].
	Grade 4	Permanently discontinue IMDELLTRA.
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Grade 3 Increased ALT or AST or bilirubin	Withhold IMDELLTRA until adverse events improve to ≤ Grade 1.
	Grade 4 Increased ALT or AST or bilirubin	Permanently discontinue IMDELLTRA.

Adverse Reactions	Severity[b]	Dosage Modification[a]
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	Permanently discontinue IMDELLTRA.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	Withhold IMDELLTRA until recovery to ≤Grade 1 or baseline. Consider permanently discontinuing if adverse reaction does not resolve within 28 days. Consider permanent discontinuation for Grade 4 events.

[a] Refer to Table 4 for dose restarting guidance.
[b] Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

2.6 Preparation

Material Compatibility Information

- IV bags composed of ethyl vinyl acetate (EVA), polyolefin, and polyvinyl chloride, (PVC) have been shown to be compatible with IMDELLTRA at the specified administration conditions.
- IV line and catheter materials composed of polyolefin, PVC, and polyurethane have been shown to be compatible with IMDELLTRA at the specified administration conditions.
- The use of Closed System Transfer Device (CSTD) is not recommended due to potential wrong dose medication error risk. Amgen has not performed compatibility testing of vial adaptor CSTDs with IMDELLTRA.

Step 1: Reconstitute IMDELLTRA with Sterile Water for Injection

- Table 8 provides the required amount of sterile water for injection required to reconstitute IMDELLTRA 1 mg and 10 mg vials.

Do not use IV Solution Stabilizer (IVSS) to reconstitute IMDELLTRA.
The IV Solution Stabilizer (IVSS) is used to coat the intravenous bag prior to addition of reconstituted IMDELLTRA to prevent adsorption of IMDELLTRA to IV bags and IV tubing.

Table 8. Required Amount of Sterile Water for Injection to Reconstitute IMDELLTRA[a]

IMDELLTRA Vial Strength	Amount of Sterile Water for Injection Needed to Reconstitute IMDELLTRA	Resulting Concentration
1 mg	1.3 mL	0.9 mg/mL
10 mg	4.4 mL	2.4 mg/mL

[a] Each vial contains overfill to allow for withdrawal of 1.1 mL (1 mg vial) or 4.2 mL (10 mg vial) after reconstitution to ensure delivery at the stated concentration of labeled vial strength.

- Using a needle and syringe filled with the required amount of sterile water, inject the sterile water against the glass vial. Avoid injecting the water directly onto the powder to prevent foaming.
- Gently swirl the contents to mix. Do not shake.
- Inspect parenteral drug products for particulate matter and discoloration prior to administration. Inspect that the solution is clear to opalescent, colorless to slightly yellow. Do not use if the solution is cloudy or has particulates.
- Further dilute reconstituted IMDELLTRA.
- The reconstituted IMDELLTRA must be further diluted within 4 hours of reconstitution or discarded.

Prepare the infusion bag: Steps 2 to 5

Step 2: Withdraw 0.9% Sodium Chloride for Injection

- Using a 250 mL prefilled bag of 0.9% Sodium Chloride for Injection, withdraw the amount of sodium chloride specified in Table 9 and discard.

Table 9. Required Amount of 0.9% Sodium Chloride to Withdraw from 250 mL IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of 0.9% Sodium Chloride to Withdraw From 250 mL IV Bag
1 mg	1 mg	14 mL
10 mg	10 mg	17 mL

Step 3: Add IV Solution Stabilizer to the infusion bag

- Inject 13 mL of IV Solution Stabilizer (IVSS) into the 250 mL 0.9% Sodium Chloride infusion bag, see Table 10.
- Gently mix the contents of the infusion bag to avoid foaming. Do not shake.

Table 10. Required Amount of IV Solution Stabilizer (IVSS) to Add to IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of IV Solution Stabilizer (IVSS) to Add to IV Bag
1 mg	1 mg	13 mL
10 mg	10 mg	13 mL

Step 4: Dilute the reconstituted IMDELLTRA into the infusion bag

- Transfer the required volume of reconstituted IMDELLTRA listed in Table 11 to the infusion bag *(containing IV Solution Stabilizer).*

NOTE: the final concentrations for the different strength vials are NOT the same following reconstitution and further dilution.

Table 11. Required Amount of Reconstituted IMDELLTRA to Add to 250 mL IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of Reconstituted IMDELLTRA to Add to 250 mL IV Bag
1 mg	1 mg	1.1 mL
10 mg	10 mg	4.2 mL

- Gently mix the contents of the bag. Do not shake.

Step 5: Remove air from IV bag

Remove air from the prepared IV bag using an empty syringe to avoid foaming.

Step 6: Prime IV tubing

- Prime intravenous tubing with either 0.9% Sodium Chloride for Injection or with the final prepared product.
- See Table 12 for maximum storage time of prepared IMDELLTRA infusion.

Prepared IMDELLTRA Infusion Bag Storage Requirements

- Administer reconstituted and diluted IMDELLTRA immediately.
- Table 12 displays the maximum storage time for the prepared IMDELLTRA infusion bag.
- Maximum storage time includes total duration from the time of reconstitution of the vial of IMDELLTRA to the end of the infusion.

Table 12. Maximum Storage Time

	Room Temperature 20°C to 25°C	Refrigerated 2°C to 8°C
Prepared IMDELLTRA Infusion Bag	8 hours	7 days
• Discard IMDELLTRA infusion after maximum storage time (from time of reconstitution). • Do not re-refrigerate prepared infusion bag.		

3 DOSAGE FORMS AND STRENGTHS

For injection: 1 mg of white to slightly yellow lyophilized powder in a single-dose vial for reconstitution and further dilution.

For injection: 10 mg of white to slightly yellow lyophilized powder in a single-dose vial for reconstitution and further dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

IMDELLTRA can cause cytokine release syndrome (CRS) including serious or life-threatening reactions.

In the pooled safety population *[see Adverse Reactions (6.1)],* CRS occurred in 55% of patients who received IMDELLTRA, including 34% Grade 1, 19% Grade 2, 1.1% Grade 3 and 0.5% Grade 4. Recurrent CRS occurred in 24% of IMDELLTRA-treated patients including 18% Grade 1 and 6% Grade 2.

Most events (43%) of CRS occurred after the first dose with 29% of patients experiencing any grade CRS after the second dose and 9% of patients experiencing CRS following the third dose or later. Following the Day 1, Day 8, Day 15 infusions, 16%, 4.3%, and 2.1% of patients experienced ≥ Grade 2 CRS, respectively. The median time to onset of all grade CRS from most recent dose of IMDELLTRA was 13.5 hours (range: 1 to 268 hours). The median time to onset of ≥ Grade 2 CRS from most recent dose of IMDELLTRA was 14.6 hours (range: 2 to 566 hours).

Clinical signs and symptoms of CRS included pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea and vomiting. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Administer IMDELLTRA following the recommended step-up dosing and administer concomitant medications before and after Cycle 1 IMDELLTRA infusions as described in Table 3 to reduce the risk of CRS *[see Dosage and Administration (2.3)].* Administer IMDELLTRA in an appropriate health care facility equipped to monitor and manage CRS. Ensure patients are well hydrated prior to administration of IMDELLTRA.

Closely monitor patients for signs and symptoms of CRS during treatment with IMDELLTRA. At the first sign of CRS, immediately discontinue IMDELLTRA infusion, evaluate the patient for hospitalization and institute supportive care based on severity. Withhold or permanently discontinue IMDELLTRA based on severity *[see Dosage and Administration (2.5)].* Counsel patients to seek medical attention should signs if symptoms of CRS occur.

5.2 Neurologic Toxicity Including ICANS

IMDELLTRA can cause serious or life-threatening neurologic toxicity, including ICANS.

In the pooled safety population *[see Adverse Reactions (6.1)],* neurologic toxicity including ICANS, occurred in 47% of patients who received IMDELLTRA, including 10% Grade 3. The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%), insomnia (6%), muscular weakness (3.7%), delirium (2.1%), syncope (1.6%) and neurotoxicity (1.1%).

ICANS occurred in 9% of IMDELLTRA-treated patients *[see Adverse Reactions (6.1)].* Recurrent ICANS occurred in 1.6% of patients. Most patients experienced ICANS following cycle 2 day 1 (24%). Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5% and 3.7% of patients experienced ≥ Grade 2 ICANS, respectively. The median time to onset of ICANS from the first dose of IMDELLTRA was 29.5 days (range: 1 to 154 days). ICANS can occur several weeks following administration of IMDELLTRA. The median time to resolution of ICANS was 33 days (range: 1 to 93 days).

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

Patients receiving IMDELLTRA are at risk of neurologic adverse reactions and ICANS resulting in depressed level of consciousness. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, in the event of any neurologic symptoms until they resolve.

Closely monitor patients for signs and symptoms of neurologic toxicity and ICANS during treatment. At the first sign of ICANS, immediately evaluate the patient and provide supportive therapy based on severity. Withhold IMDELLTRA or permanently discontinue based on severity *[see Dosage and Administration (2.5)].*

5.3 Cytopenias

IMDELLTRA can cause cytopenias including neutropenia, thrombocytopenia, and anemia.

In the pooled safety population, *[see Adverse Reactions (6.1)],* decreased neutrophils occurred in 12% including 6% Grade 3 or 4 of IMDELLTRA-treated patients. The median time to onset for Grade 3 or 4 neutropenia was 29.5 days (range: 2 to 213). Decreased platelets occurred in 33% including 3.2% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased platelets was 50 days (range: 3 to 420). Decreased hemoglobin occurred in 58% including 5% Grade 3 or 4. Febrile neutropenia occurred in 0.5% of patients treated with IMDELLTRA.

Monitor patients for signs and symptoms of cytopenias. Perform complete blood counts prior to treatment with IMDELLTRA, before each dose, and as clinically indicated. Based on the severity of cytopenias, temporarily withhold, or permanently discontinue IMDELLTRA *[see Dosage and Administration (2.5)].*

5.4 Infections

IMDELLTRA can cause serious infections, including life-threatening and fatal infections.

In the pooled safety population, *[see Adverse Reactions (6.1)],* infections including opportunistic infections occurred in 41% of patients who received IMDELLTRA. Grade 3 or 4 infections occurred in 13% of patients. The most frequent infections were COVID-19 (9%, majority during the COVID-19 pandemic), urinary tract infection (10%), pneumonia (9%), respiratory tract infection (3.2%), and candida infection (3.2%). Monitor patients for signs and symptoms of infection prior to and during treatment with IMDELLTRA and treat as clinically indicated. Withhold or permanently discontinue IMDELLTRA based on severity *[see Dosage and Administration (2.5)].*

5.5 Hepatotoxicity

IMDELLTRA can cause hepatotoxicity.

In the pooled safety population *[see Adverse Reactions (6.1)],* elevated ALT occurred in 42% with Grade 3 or 4 ALT elevation occurring in 2.1% of IMDELLTRA-treated patients. Elevated AST occurred in 44% of patients, with Grade 3 or 4 AST elevation occurring in 3.2%. Elevated bilirubin occurred in 15% of patients, with Grade 3 or 4 total bilirubin elevations occurred in 1.6% of patients *[see Adverse Reactions (6.1)].* Liver enzyme

elevation can occur with or without concurrent CRS. Monitor liver enzymes and bilirubin prior to treatment with IMDELLTRA, before each dose, and as clinically indicated. Withhold IMDELLTRA or permanently discontinue based on severity *[see Dosage and Administration (2.5)].*

5.6 Hypersensitivity

IMDELLTRA can cause severe hypersensitivity reactions.

Clinical signs and symptoms of hypersensitivity may include, but are not limited to, rash and bronchospasm. Monitor patients for signs and symptoms of hypersensitivity during treatment with IMDELLTRA and manage as clinically indicated. Withhold or consider permanent discontinuation of IMDELLTRA based on severity *[see Dosage and Administration (2.5)]*.

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose *[see Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome (CRS) *[see Warnings and Precautions (5.1)]*
- Neurologic Toxicity Including ICANS *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Infections *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Extensive Stage Small Cell Lung Cancer

The pooled safety population described in the WARNINGS AND PRECAUTIONS and below reflects exposure to intravenous IMDELLTRA, as a single agent, at the recommended dosage of IMDELLTRA 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8 and 15, and then every 2 weeks until disease progression or intolerable toxicity

in 187 patients with extensive stage small cell lung cancer enrolled in Study DeLLphi-300 and Study DeLLphi-301. Among 187 patients who received IMDELLTRA, 31% were exposed for 6 months or longer and 14% were exposed for greater than one year.

The most common (>20%) adverse reactions were cytokine release syndrome (55%), fatigue (51%), pyrexia (36%), dysgeusia (36%), decreased appetite (34%), musculoskeletal pain (30%), constipation (30%), anemia (27%) and nausea (22%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (57%), decreased sodium (16%), increased uric acid (10%), decreased total neutrophils (6%), decreased hemoglobin (5%), increased activated partial thromboplastin time (5%), decreased potassium (5%), increased aspartate aminotransferase (3.2%), decreased white blood cells (3.8%), decreased platelets (3.2%) and increased alanine aminotransferase (2.1%).

The demographic characteristics of patients who received IMDELLTRA were: median age 66 years (range: 35 to 82); 65% male; 70% White, 26% Asian, 2.1% Black or African American; and 2.1% Hispanic or Latino.

Serious adverse reactions occurred in 58% of patients who received IMDELLTRA. Serious adverse reactions in >3% of patients included cytokine release syndrome (24%), pneumonia (6%), pyrexia (3.7%) and hyponatremia (3.6%). Fatal adverse reactions occurred in 2.7% of patients who received IMDELLTRA including pneumonia 0.5%, aspiration (0.5%), pulmonary embolism (0.5%), respiratory acidosis (0.5%), and respiratory failure (0.5%).

Permanent discontinuation of IMDELLTRA due to an adverse reaction occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of IMDELLTRA in >1% of patients included cytokine release syndrome (1.6%) and tumor lysis syndrome (1.1%).

Dosage interruptions of IMDELLTRA due to an adverse reaction occurred in 27% of patients. Adverse reactions which required dosage interruption in ≥2% of patients included fatigue (3.2%), cytokine release syndrome (2 .7%) and respiratory tract infection (2.1%).

Table 13 summarizes adverse reactions observed in Study DeLLphi-300 and Study DeLLphi-301.

Table 13. Adverse Reactions (≥ 15%) in Patients with ES-SCLC Who Received IMDELLTRA in Study DeLLphi-300 and Study DeLLphi-301

Adverse Reaction	IMDELLTRA[a] (N = 187)	
	Any Grade (%)	Grade 3 or 4 (%)
Immune system disorders		
Cytokine release syndrome[b]	55	1.6
General disorders and administration site conditions		
Fatigue[c]	51	10
Pyrexia	36	0
Nervous system disorders		
Dysgeusia	36	0
Metabolism and nutrition disorders		
Decreased appetite	34	2.7
Nausea	22	1.6
Gastrointestinal disorders		
Constipation	30	0.5
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[d]	30	1.1
Blood and Lymphatic System Disorders		
Anemia	27	6
Respiratory, thoracic and mediastinal disorders		
Dyspnea[e]	17	2.1
Cough	17	0

[a] Graded using CTCAE Version 4.0 and Version 5.0.
[b] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019.
[c] Includes fatigue and asthenia.
[d] Includes myalgia, arthralgia, back pain, pain in extremity, neck pain, musculoskeletal chest pain, non-cardiac chest pain and bone pain.
[e] Includes dyspnea and exertional dyspnea.

Table 14 summarizes laboratory abnormalities in Study DeLLphi-300 and Study DeLLphi-301.

Table 14. Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with ES - SCLC in Study DeLLphi-300 and Study DeLLphi-301

Laboratory Abnormality	IMDELLTRA[a]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased lymphocytes	84	57
Decreased hemoglobin	58	5
Decreased white blood cells	44	3.8
Decreased platelets	33	3.2

Laboratory Abnormality	IMDELLTRA[a]	
	All Grades (%)	Grade 3 or 4 (%)
Decreased neutrophils[b]	12	6
Chemistry		
Decreased sodium	68	16
Decreased potassium	50	5
Increased aspartate amino transferase	44	3.2
Increased alanine aminotransferase	42	2.1
Decreased magnesium	33	1.6
Increased creatinine	29	0.5
Increased sodium	26	0.0
Increased alkaline phosphate	22	0.0

[a] The denominator used to calculate the rate varied from 41 to 187 based on the number of patients with a baseline value and at least one post-treatment value.
[b] All Grade lab abnormalities occurring at a frequency less than 20% included decreased neutrophils.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of IMDELLTRA in pregnant women to inform a drug-associated risk.

In an animal reproduction study, a murine surrogate molecule administered intravenously to pregnant mice crossed the placental barrier.

Tarlatamab causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance.

Human immunoglobulin G (IgG) and proteins comprising IgG-derived fragment crystallizable (Fc) domains are known to cross the placental barrier; therefore, IMDELLTRA has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with tarlatamab. In an embryo-fetal developmental toxicity study, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause maternal toxicity, embryo-fetal toxicity or teratogenicity.

8.2 Lactation

Risk Summary

There are no data on the presence of tarlatamab in human milk or the effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to IMDELLTRA are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose.

8.3 Females and Males of Reproductive Potential

IMDELLTRA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating IMDELLTRA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of IMDELLTRA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 187 patients with SCLC who received IMDELLTRA 10 mg as a single agent, 54% were 65 years of age or older and 12% were 75 years of age or older. No overall

differences in IMDELLTRA pharmacokinetics, or safety were observed between older patients (≥ 65 years of age) and younger patients. Clinical studies of IMDELLTRA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

Tarlatamab is a bispecific DLL3-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T cells. Tarlatamab is produced using recombinant DNA technology in Chinese hamster ovary cells. It consists of 982 amino acids and has a molecular weight of approximately 105 kilodaltons.

IMDELLTRA (tarlatamab) for injection is supplied as a sterile, preservative-free, white to slightly yellow, lyophilized powder in a single-dose vial for reconstitution and further dilution.

Each 1 mg vial contains tarlatamab (1 mg), glutamic acid (0.54 mg), polysorbate 80 (0.03 mg), sucrose (27.67 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 1.3 mL of Sterile Water for Injection the resulting concentration is 0.9 mg/mL IMDELLTRA.

Each 10 mg vial contains tarlatamab (10 mg), glutamic acid (3.2 mg), polysorbate 80 (0.2 mg), sucrose (172.0 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 4.4 mL of Sterile Water for Injection the resulting concentration is 2.4 mg/mL IMDELLTRA.

IV Solution Stabilizer is supplied as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each vial of IV Solution Stabilizer contains citric acid monohydrate (36.75 mg), lysine hydrochloride (1598.8 mg), polysorbate 80 (7 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tarlatamab is a bispecific T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T-cells. Tarlatamab causes T-cell activation, release of inflammatory cytokines, and lysis of DLL3-expressing cells. Tarlatamab had anti-tumor activity in mouse models of SCLC.

12.2 Pharmacodynamics

<u>Exposure-Response Relationships</u>

There are no clinically significant exposure-response relationships for efficacy over the exposure range observed between tarlatamab 10 mg and 100 mg (10 times the highest approved recommended dosage).

There is an exposure-response relationship between tarlatamab exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure.

Serum Cytokines
Transient elevation of serum cytokines IL-2, IL-6, IL-8, IL-10, and IFN-γ were observed at a tarlatamab dosage of 0.3 mg and above. Peak elevation of cytokines was generally observed 24 hours following the initial dose of IMDELLTRA at 1 mg on Cycle 1 Day 1 and generally returned to baseline levels prior to the next infusion on Cycle 1 Day 8.

12.3 Pharmacokinetics

Tarlatamab pharmacokinetic parameters are presented as geometric mean (CV%) unless otherwise specified. The exposure of tarlatamab increased dose proportionally in the evaluated dose range of IMDELLTRA 1 mg to 100 mg every 2 weeks (10 times the highest approved recommended dosage). Tarlatamab steady state exposures were achieved by Cycle 2 Day 15. Pharmacokinetic exposures are summarized for the recommended dosage of IMDELLTRA in Table 15.

Table 15. Pharmacokinetic Parameters of Tarlatamab

	Parameter[a]		
	C_{avg} (ng/mL)	**C_{max}** (ng/mL)	**C_{trough}** (ng/mL)
First step-up dose 1 mg	102 (29%)	285 (41%)	47 (38%)
First treatment dose 10 mg	1050 (29%)	2900 (41%)	502 (39%)
Steady state 10 mg every 2 weeks	1040 (44%)	3400 (40%)	495 (73%)

[a] Parameters are reported as geometric mean (CV%).

Distribution
Tarlatamab steady state volume of distribution is 8.6 L (18.3%).

Metabolism
Tarlatamab is expected to be metabolized into small peptides by catabolic pathways.

Elimination
Tarlatamab's median terminal elimination half-life (min, max) is 11.2 (4.3 to 26.5) days and the estimated systemic clearance is 0.65 L/day (44%) in patients with SCLC.

Specific Populations
No clinically significant differences in the pharmacokinetics of tarlatamab were observed based on age (32 to 82 years), body weight (35 to 149 kg), sex, race (White and Asian), mild or moderate renal impairment (eGFR ≥ 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN).

The effects of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR <15 mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN, any AST) on the pharmacokinetics of tarlatamab are unknown.

Effects of Tarlatamab on CYP450 Substrates
Tarlatamab causes transient release of cytokines that may suppress CYP450 enzymes and may result in an increased exposure of concomitant CYP substrates during and up to 14 days after occurrence of cytokine release syndrome *[see Clinical Pharmacology (12.2)]*.

12.6 Immunogenicity

The observed incidence of antidrug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of tarlatamab or of other tarlatamab products.

In Study DeLLphi-301, of the patients who received recommended step-up and full dosage of IMDELLTRA and were evaluable for presence of ADA against tarlatamab, 3.2% (4/124) of patients tested positive for anti-tarlatamab antibodies and none of the patients developed neutralizing antibodies against tarlatamab based on a cell-based bioassay. Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and effectiveness of tarlatamab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with tarlatamab.

No studies have been conducted to evaluate the effects of tarlatamab on fertility.

14 CLINICAL STUDIES

14.1 Small Cell Lung Cancer

The efficacy of IMDELLTRA was evaluated in Study DeLLphi-301 [NCT05060016], an open-label, multicenter, multi-cohort clinical trial. Eligible patients were required to have relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy, an ECOG Performance Status of 0 or 1, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) The trial excluded patients with symptomatic brain metastases, evidence of interstitial lung disease or non-infectious pneumonitis, and active immunodeficiency.

A total of 99 patients received IMDELLTRA intravenously at an initial dose of 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter until disease progression or unacceptable toxicity.

The study population characteristics were: median age 64 years (range: 35 to 82); 48% of patients ≥65 years and 10% of patients ≥75 years; 72% male; 58% White, 41% Asian; 1% Hispanic or Latino; and 74% have ECOG 1.

Ninety-seven percent of patients had metastatic disease at baseline; 22% had brain metastases at baseline; and 92% were former/current smokers. All patients received prior platinum-based chemotherapy (median two lines); 74% received prior anti-PD-(L)1 therapy (including 59% who received anti-PD[L]1 therapy in combination with platinum-based chemotherapy in the frontline setting); 51% received prior topoisomerase I inhibitor (including 20% who received topotecan). Platinum sensitivity status, defined by time to progression after first line platinum therapy, was known for 69/99 patients. Twenty-seven patients (27%) had platinum-resistant SCLC, defined as time to progression < 90 days after first line platinum therapy, while 42 patients (42%) had platinum-sensitive SCLC.

Tumor assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to RECIST v1.1.

Efficacy results are presented in Table 16.

Table 16. Efficacy Results for Study DeLLphi-301

Efficacy Parameter	IMDELLTRA (N = 99)
Overall Response Rate (ORR)	
ORR, % (95% CI)[a]	40 (31, 51)
Complete Response, n (%)	2 (2)
Partial Response, n (%)	38 (38)
Duration of Response (DOR)[a]	
Median[b], months (range)	9.7 (2.7, 20.7+)

Duration ≥ 6 months[c], %	68
Duration ≥ 12 months[c], %	40

[a] Assessed by Blinded Independent Central Review, CI= Confidence Interval
[b] Median based on Kaplan-Meier estimate.
[c] Based on observed duration of response.

Of the 69 patients with available data regarding platinum sensitivity status, the ORR was 52% (95% CI 32, 71) in 27 patients with platinum-resistant SCLC and 31% (95% CI 18, 47) in 42 patients with platinum-sensitive SCLC.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

IMDELLTRA (tarlatamab) for injection is a sterile, preservative-free, white to slightly yellow, lyophilized powder supplied as follows:

- 1 mg package contains 1 single-dose vial (type 1 glass vial with elastomeric stopper, aluminum seal and flip-off cap) of 1 mg IMDELLTRA and 2 vials (type 1 glass vial with elastomeric stopper, aluminum seal and flip-off cap) of 7 mL IV Solution Stabilizer.
- 10 mg package contains 1 single-dose vial (type 1 glass vial with elastomeric stopper, aluminum seal and flip-off cap) of 10 mg IMDELLTRA and 2 vials (type 1 glass vial with elastomeric stopper, aluminum seal and flip-off cap) of 7 mL IV Solution Stabilizer.

Not all presentations may be marketed.

16.2 Storage and Handling

Store IMDELLTRA and IV Solution Stabilizer (IVSS) vials refrigerated at 2°C to 8°C in the original carton to protect from light until time of use. Do not freeze.
IMDELLTRA and IV Solution Stabilizer (IVSS) vials may be kept at room temperature between 20°C to 25°C for up to 24 hours in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Cytokine Release Syndrome (CRS)

Advise patients of the risk of CRS, and to immediately contact their healthcare provider for signs and symptoms associated with CRS including pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea and vomiting *[see Warnings and Precautions (5.1)]*.

Advise patients that they should be monitored from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting *[see Warnings and Precautions (5.1)].*

Advise patients to remain within 1-hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.

Neurologic Toxicity Including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Discuss the signs and symptoms associated with ICANS. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of ICANS, such as encephalopathy, confusion, delirium, seizure, ataxia, weakness or numbness of arms and legs, tremor, and headache.

Advise patients who experience neurologic toxicity or symptoms of ICANS to refrain from driving or operating heavy or potentially dangerous machinery and engaging in hazardous occupations or activities during treatment with IMDELLTRA *[see Warnings and Precautions (5.2)]*.

Cytopenias

Discuss the signs and symptoms associated with cytopenias, including neutropenia and febrile neutropenia, anemia, and thrombocytopenia *[see Warnings and Precautions (5.3)].* Inform patients that they will need to undergo lab tests to monitor blood counts. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of cytopenias.

Infections

Discuss the signs and symptoms of infections. Advise patients of the risk of serious infections, and to immediately contact their healthcare provider for signs or symptoms of infections *[see Warnings and Precautions (5.4)].*

Hepatotoxicity

Discuss the signs and symptoms of hepatotoxicity. Inform patients that they will need to undergo lab tests to monitor liver function. Advise patients to immediately contact their healthcare provider for signs and symptoms of liver dysfunction *[see Warnings and Precautions (5.5)].*

Hypersensitivity

Discuss the signs and symptoms of allergic reactions. Advise patients to immediately seek medical attention for any signs and symptoms of severe reactions *[see Warnings and Precautions (5.6)].*

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose *[see Use in Specific Populations (8.2)].*

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