

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761344Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 02, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761344
Product Name, Dosage Form, and Strength:	Imdelltra (tarlatamab-dlle) for injection, 1 mg/vial and 10 mg/vial
Applicant Name:	Amgen Inc.
FDA Received Date:	April 24, 2024, April 26, 2024
TTT ID #:	2023-6460-1
DMEPA 2 Safety Evaluator:	Farinaz Beniesfahany, PharmD
DMEPA 2 Team Leader:	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

Amgen Inc. submitted revised carton labeling on April 24, 2024 and revised container labels on April 26, 2024 for Imdelltra. The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Imdelltra (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Amgen Inc. implemented our recommendations with the exception of the recommendation regarding the format of the expiration date. Amgen Inc. proposed to use the expiration date format “DDMMYYYY” which per Amgen Inc. is consistent with their currently approved products. We find Amgen Inc.’s rationale acceptable from a medication error perspective. We have no additional recommendations at this time.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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^a Beniesfahany, F. Human Factors Study Report and Label and Labeling Review for Imdelltra (BLA 761344). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 06. TTT ID: 2023-6728, 2023-6460.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: April 30, 2024

To: Ashley Lane, Regulatory Project Manager
Division of Oncology 2 (DO2)

Barbara Scepura, Associate Director for Labeling, DO2

From: Kelle Caruso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for IMDELLTRA™ (tarlatamab-xxxx) for injection, for intravenous use

BLA: 761344

Background:

In response to DO2's consult requests dated November 12, 2023 and April 23, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA submission for IMDELLTRA™ (tarlatamab-xxxx) for injection, for intravenous use.

PI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 19, 2024, and our comments are provided below.

Medication Guide:

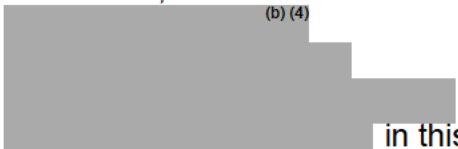
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on April 24, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on April 19, 2024 and the updated container labels accessed from SharePoint on April 23, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Kelle Caruso at (301) 796-5044 or Kelle.Caruso@fda.hhs.gov.

PI:

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comments</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION	“This indication is approved under accelerated approval based on <u>overall</u> response rate and duration of response . . .” (Underlined emphasis added).	OPDP notes that according to section 14, the efficacy of Imdelltra was based on <u>overall</u> response rate and duration of response. We also note that Section 1 of the USPI still says “This indication is approved under accelerated approval based on <u>overall</u> response rate and duration of response” For accuracy and consistency with Sections 1 and 14, we recommend keeping the word “overall” in the indication section of the HL. We defer to DO2.
	“Infections: (b) (4)  Monitor for signs and symptoms of infection; treat appropriately. Withhold or permanently discontinue based on severity. (5.4)” (Underlined emphasis added).	If accurate, OPDP recommends (b) (4)  in this W&P for Infections in the HL. When it comes to the communication of these risks in promotional materials, having this direct statement of risk upfront helps us to ensure the nature and severity of the risk is being clearly communicated. This is especially impactful in shorter promotional communications, which are often modeled after the information in the HL, and may not include the entirety of the warning.
	“Hypersensitivity: (b) (4)  Monitor for signs and symptoms of hypersensitivity	If accurate, OPDP recommends (b) (4)  in this W&P for Hypersensitivity in the HL. When it comes to the

	and treat accordingly. Withhold or permanently discontinue based on severity. (5.6)” (Underlined emphasis added).	communication of these risks in promotional materials, having this direct statement of risk upfront helps us to ensure the nature and severity of the risk is being clearly communicated. This is especially impactful in shorter promotional communications, which are often modeled after the information in the HL, and may not include the entirety of the warning.
6.1 Clinical Trials Experience	“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%)”	OPDP notes that according to Table 13, Nausea occurred in 22% of patients, which meets the >20% threshold for most common adverse reactions. We recommend adding “nausea (22%)” to the list of most common adverse reactions here in Section 6.1 as well as in the HL.
12.2 Pharmacodynamics	“Serum Cytokines Transient elevation of serum cytokines IL-2, IL-6, IL-8, IL-10, and IFN-γ were observed at a tarlatamab-xxxx dosage of 0.3 mg and above. Peak elevation of cytokines was <u>generally</u> observed 24 hours following the initial dose of IMDELLTRA at 1 mg on Cycle 1 Day 1 and <u>generally</u> returned to baseline levels prior to the next infusion on Cycle 1 Day 8.” (underlined emphasis added).	We note that the term “generally” is vague. Consistent with the recommendations made in the <i>Labeling Review Tool</i> to avoid nonspecific quantitative terms, OPDP recommends revising to include the specific quantitative information, if available, for context here. We defer to DO2 on whether this is necessary in this section.
14 CLINICAL STUDIES	“The efficacy of IMDELLTRA was evaluated in Study DeLLphi-301 [NCT05060016], an open-label, multicenter trial.”	OPDP notes that the efficacy of Imdelltra was evaluated in a single-arm trial . For accuracy in describing the trial design in the label and subsequently in promotional materials, would

		DO2 consider adding the term “single-arm trial” to the trial description in this section? When taken out of context and used in promotional materials, this may help the audience more clearly understand any potential limitations of the trial design. We note that “single-arm trial” seems to generally be included in other NSCLC drug labels when accurate/appropriate. However, we defer to DO2 on whether this is appropriate/necessary.
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Carton and Container:

<u>Applicable Strength</u>	<u>Statement from Proposed Carton/Container (if applicable)</u>	<u>OPDP Comment</u>
1mg and 10mg	“IMDELLTRA (tarlatamab-dlle) For injection”	The established name with suffix appears cramped and difficult to read compared to the proprietary name. OPDP recommends revising the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, ‘[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.’

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/s/

KELLE E CARUSO
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 24, 2024

To: Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Oncology II (DO2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Laurie Buonaccorsi, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kelle Caruso, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): IMDELLTRA (tarlatamab-dlle)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761344

Applicant: Amgen Inc.

1 INTRODUCTION

On October 12, 2023, Amgen Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761344 for IMDELLTRA (tarlatamab-dlle) for injection, with a proposed indication of monotherapy for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on November 12, 2023 for DMPP and OPDP to review the Applicant's proposed (b) (4) for IMDELLTRA (tarlatamab-dlle) for injection.

On March 29, 2024, DO2 requested that the Applicant revise (b) (4) Medication Guide (MG) due to proposed revisions made to the Prescribing Information (PI) that incorporated a Boxed Warning highlighting serious risks regarding cytokine release syndrome and neurotoxicity, of which patients should be made aware. On April 3, 2024, the Applicant resubmitted the proposed (b) (4) MG.

2 MATERIAL REVIEWED

- Draft IMDELLTRA (tarlatamab-dlle) for injection MG received on April 3, 2024, and received by DMPP and OPDP on April 19, 2024.
- Draft IMDELLTRA (tarlatamab-dlle) for injection Prescribing Information (PI) received on October 12, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 19, 2024.
- Approved ELREXFIO (elranatamab-bcmm), EPKINLY (epcoritamab-bysp), TECVAYLI (teclistamab-cqyv), TALVEY (talquetamab-tgvs), and LUNSUMIO (mosunetuzumab-axgb) injection comparator labeling dated August 14, 2023, May 19, 2023, February 20, 2024, August 8, 2023, and December 22, 2022

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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KELLE E CARUSO
04/24/2024 10:03:16 AM

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04/24/2024 10:39:29 AM

Clinical Inspection Summary

Date	March 26, 2024
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Yufan Liu, Clinical Analysts Amy Barone, MD, Team Leader (CDTL) Erin Larkins, MD, Supervisory Associate Division Director Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	BLA761344
Applicant	Amgen, Inc.
Drug	Tarlatamab (b) (4)
NME (Yes/No)	Yes
Therapeutic Classification	Monoclonal Antibody
Proposed Indication(s)	Treatment of patients (b) (4) small cell lung cancer (SCLC) with disease progression on or after platinum-based therapy (b) (4)
Consultation Request Date	November 17, 2023
Summary Goal Date	March 29, 2024
Action Goal Date	May 16, 2024
PDUFA Date	June 12, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study DeLLphi-301 (20200491) were submitted to the Agency in support of Biologics License Application (BLA 761344) for tarlatamab for the treatment of patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Three clinical investigators (CI), Drs. Myung-Ju Ahn, (Site ID #66264), Byoung Chul Cho (Site ID #25054), and Enriqueta Felip Font (Site ID #29404), as well as the imaging Contract Research Organization (CRO) (b) (4) were inspected.

As previously communicated to the Division, the inspection of CI Myung-Ju Ahn revealed protocol violations, namely, enrollment of 2 subjects who did not meet eligibility criteria and underreporting of adverse events. Specifically, Subject (b) (6) had a new diagnosis of adenocarcinoma and should not have been enrolled in the study, as the subject did not fulfill inclusion criterion to have “histologically or cytologically confirmed relapse/refractory SCLC.” We recommend excluding data from this subject from efficacy analysis. Subject # (b) (6) had abdominal aneurysm with thrombosis and should have been excluded from study based on the exclusion criteria. Based on the available information, this protocol deviation did not seem to have

impact on this subject's safety.

Inspection of Dr. Ahn's site also revealed underreporting of adverse events in 14 out of 19 subjects enrolled at the site. A total of 61 AEs including three Grade 3 AEs and two Grade 5 AEs (death due to underlying disease) were not reported to the BLA in the sponsor's data listings. The root cause of the violations is due to lack of human resources at the site as well as failure in the Sponsor's monitoring activities. On January 31, 2024, OSI, in conjunction with the review division, requested that Amgen provide a root-cause and impact analysis for the eligibility and AE discrepancies at Dr. Ahn's site, and to perform a source record review of subject's eligibility and adverse events for all subjects enrolled at all 5 sites in S. Korea. Based on Amgen's source record review of the Korean sites, an additional 42 unreported AEs at 3 of the 4 remaining sites and involving 12 subjects were identified.

Amgen has acknowledged the deficiencies and decided to further expand their review to conduct 100% source data verification for all sites involved in Study 20200491. Upon completion, Amgen plans to submit an impact analysis of changes in the dataset on the benefit-risk profile of tarlatamab; updated data sets for Study 20200491, and revised tables, figures and listings (TFLs) for impacted data.

Inspections of CIs, Drs. Cho and Font sites also revealed unreported AEs that, as noted below, are unlikely to significantly affect overall reliability of safety or efficacy data for these sites. The large number of underreported AEs by the Korean sites, not captured during the Sponsor's monitoring activities, is a major concern and put into question the integrity of the safety data submitted to support the approval of tarlatamab for the proposed indication. OSI agrees with Amgen's plan to conduct a 100% source data verification for all clinical sites involved in the Study 20200491 (DeLLphi-301) and defer to review of the revised data to the Revision Division.

Inspection of the imaging CRO, (b) (4) revealed no significant discrepancies or regulatory violations. Based on this inspection, the data generated by (b) (4) appear acceptable in support of the proposed indication.

II. BACKGROUND

Amgen Inc. submitted BLA761344 seeking approval for tarlatamab for the above indication based on the efficacy and safety results from Study DeLLphi-301, a 3-part, phase 2, open-label, international trial in patients with advanced SCLC with disease progression after receiving previous platinum-based chemotherapy.

Study DeLLphi-301 was conducted in 3 parts. Part 1 evaluated 2 dose levels of tarlatamab in which 176 subjects were enrolled and randomized in a 1:1 ratio to receive either 10 mg or 100 mg of tarlatamab. Tarlatamab 1 mg step dose was given on cycle 1 day 1. The full dose of tarlatamab was randomized between 10 mg or 100 mg and was given on day 8 and 15 of cycle 1, and every 2 weeks (Q2W) thereafter. Administration of tarlatamab was an IV infusion for 60 minutes followed by a flush.

Part 2 was a dose expansion phase at the selected target dose based on an interim analysis of Part 1. A total of 100 subjects (from Part 1 and Part 2 combined) were enrolled at the selected target dose level of 10 mg. Part 3 was initiated after completing enrollment of Part 1 and Part 2, to enroll additional subjects at the target dose level, with modified cycle 1 monitoring criteria.

Eligible patients must have histologically or cytologically confirmed relapsed or refractory SCLC and had progressed or recurred following on platinum-based regimen and at least 1 other prior line of therapy, an ECOG performance status of 0 or 1 at baseline, and adequate organ function as specified in the protocol.

The primary objectives of the Part 1 of the study were to evaluate the safety, efficacy and pharmacokinetics of tarlatamab at 10 mg and 100 mg administered orally, daily. The primary objective and endpoint of the Part 2 was to evaluate the anti-tumor activity of tarlatamab at 10 mg, as determined by Objective Response Rate. The primary objective of Part 3 was to evaluate safety of reduced monitoring period in cycle 1 at 10 mg dose of tarlatamab. Key secondary objectives/endpoints (all Parts) were to determine, pharmacokinetics and immunogenicity of tarlatamab.

Eligible patients were to sign the informed consent before undergoing any protocol-specific procedures. Baseline clinical, laboratory and imaging scans should be performed within 21 days from the time of consent to enrollment. Tumor assessments were to be performed at Screening (within 21 days prior to enrollment), every 6 weeks from weeks 1 thru 48, then every 12 weeks thereafter until confirmed disease progression per RECIST 1.1, withdrawal of consent or start of new anticancer therapy. All scans were to be submitted to (b) (4) the imaging CRO for central review.

At the time of the data cut-off date (June 27, 2023), at total of 222 subjects had been enrolled across the 3 arms (176 subjects in Part 1, 12 in Part 2 and 34 in Part 3). The efficacy population to support the proposed indication consists of data from 99 subjects enrolled in Part 1 and 2 of the study, who received at least one dose of tarlatamab at the target dose of 10 mg. The safety population consists of 220 subjects enrolled in the study who received at least one dose of tarlatamab.

Drs. Myung-Ju Ahn (Site # 66264), Byoung Chul Cho (Site # 25054), and Enriqueta Felip Font (Site # 29404), as well as (b) (4) were inspected.

III. RESULTS (by site):

1. **Dr. Myung-Ju Ahn (Site ID #66264)**
81 Irwon-Ro, Gangnam-Gu
Seoul, NA 6351
South Korea

Inspection dates: January 22 – 26, 2024

Dr. Ahn was inspected as a routine PDUFA inspection for Study DeLLphi-301. Dr. Ahn was previously inspected in February 2017.

At the time of the inspection, the site had screened and enrolled 19 subjects in the study. Of the 19 subjects enrolled, 4 subjects were on active treatment, 12 were on long term follow-up after disease progression, 2 subjects withdrew consent, and one subject had died.

Source records for all 19 subjects were reviewed. Records reviewed included: informed consent forms, medical records, eligibility criteria, investigational drug administration, adverse events reporting, protocol deviations, and subject dispositions. Records were compared with data listing tables submitted to the BLA.

The following **protocol deviations** were observed and previously communicated by OSI to the review division via email on January 28, 2024.

1. Subjects enrolled despite not meeting Eligibility Criteria

- Subject (b) (6) did not meet protocol inclusion criterion 103, which requires for subject to have “*histologically or cytologically confirmed relapsed/refractory SCLC*”. The subject was a 65-year-old male who was referred from another hospital with the diagnosis of small cell carcinoma, and had progressed following prior therapy with platinum, etoposide and atezolizumab for SCLC. Since an archived tumor sample was not available for confirmation, a biopsy was conducted at the site which revealed adenocarcinoma. The subject was enrolled into Part 1 of the study and received tarlatamab 100mg from (b) (6). Treatment was discontinued per investigator’s decision and subject died to disease progression on (b) (6).

Reviewer’s comment: With the biopsy report of adenocarcinoma, the subject should not have been enrolled in the investigational trial with tarlatamab. Dr. Ahn claimed that “it would be rare for a small cell carcinoma to transform into non-small cell carcinoma/adenocarcinoma and that in her “clinical judgement, the treatment (with tarlatamab) would be their best option because it was progressing rapidly”. It is noted that no effort was made by the site to confirm the diagnosis of adenocarcinoma, to obtain genomic tumor markers or to consider a second primary, either from lung or another organ sites (e.g., breast or colon cancer), which could potentially offer alternative standard of care therapy for this subject.

In her response to FDA’s form 483 dated February 27, 2024, Dr. Ahn acknowledged the protocol deviation and the need to consult with the Sponsor concerning this subject’s eligibility assessment.

OSI recommends excluding data from this subject from all efficacy analysis.

- Subject (b) (6) did not meet protocol exclusion criterion 207, which excludes subjects with “history of arterial thrombosis...within 12 months of first dose of tarlatamab”. Baseline CT scan of the abdomen (07/15/22) showed the presence of an abdominal aneurysm with thrombosis, which was confirmed by subsequent follow-up scans measuring a maximum diameter of 4.1cm on 12/12/2022. The subject was enrolled into Part 1 of the study and received tarlatamab 10 mg from August 2, 2022, thru June 21, 2023. No apparent adverse events were reported.

Reviewer’s comment: Reports from repeated CT scans of the abdomen indicate that the subject had an aortic aneurysm with thrombosis. Dr. Ahn stated that the subject was one of her sub-investigator’s patients and that she trusted the judgement of the sub-investigator who felt this was not a true thrombosis. She further stated that this was a case of dissection without thrombosis and was not sure the patient should be excluded. Where the radiology report and the sub-investigator’s conclusion differed, it was not contemporaneously documented, nor was there a discussion with the medical monitor regarding eligibility.

In her response to FDA’s form 483 dated February 27, 2024, a follow-up CT angiography on 2/2/24 to assess the current status of the aortic aneurysm and identified no change in size of any complication such as thrombosis. Corrective and preventive actions to be taken include retraining relating to ALCOA principles and ensure that where questions arise from the available objective documentations, any subject’s eligibility assessment will be fully documented by the investigator.

Based on the available information, the above protocol deviation did not impact on the subject’s safety.

2. Unreported Adverse Events:

Underreporting of adverse events was observed in 14 out of 19 subjects enrolled at the site. The following AEs were not captured in the electronic data capture (EDC) database until the first day of the inspection, therefore, not reported to the BLA.

Table 1. AEs not Reported to the BLA (CI Myung-Ju Ahn, SITE ID # 66264)

Subject ID#	Adverse Event	Date of the Event	Serious (Y/N)	Grade	AE outcome
(b) (6)	Pleural effusion	(b) (6)	N	2	Recovered/Resolved
	Anemia		N	2	Recovered/Resolved
	Pruritus		N	1	Not recovered/Not resolved
	Myalgia		N	1	Not recovered/Not resolved
	Both knee pain		N	1	Not recovered/Not resolved
	Hypothyroidism		N	2	Not recovered/Not resolved
	Itching whole body		N	1	
	Cytokine release syndrome		N	1	Recovered/Resolved
	Hyponatremia		N	2	Not recovered/Not resolved
	Vomiting				
	Myalgia				
	Cytokine release syndrome		N	1	Recovered/Resolved
	Cytokine release syndrome		N	1	Recovered/Resolved
	Hypophosphatemia		N	2	Recovered/Resolved
	Hypocalcemia		N	2	Recovered/Resolved
	Hypoalbuminemia		N	2	Recovered/Resolved
	Progression of SCLC		Y	5	Fatal
	Drug induced pneumonitis		Y	3	Not recovered/Not resolved
	Oral candidiasis		N	2	Recovered/Resolved
	Progression of SCLC		Y	5	Fatal
	Nausea		N	1	Recovered/Resolved
	Anorexia		N	1	
	Nausea		N	2	Recovered/Resolved
	Myalgia		N	1	Recovered/Resolved
	Nausea		N	2	Recovered/Resolved
	Fever		N	1	Recovered/Resolved
	Right ankle pain		N	2	Recovered/Resolved
	Oral mucositis		N	1	Recovered/Resolved
	Pulmonary embolism		N	2	Not recovered/Not resolved
	Herpes zoster		N	2	Recovered/Resolved
	Dyslipidemia		N	1	Not recovered/Not resolved
	Hemoptysis		N	2	Recovered/Resolved
	Constipation		N	2	Not recovered/Not resolved
	Aspartate aminotransferase increased		N	2	Recovered/Resolved

	Alanine aminotransferase increased	(b) (6)	N	2	Recovered/Resolved
	Hypothyroidism		N	1	
(b) (6)	Nausea		N	1	Not recovered/Not resolved
	Multifocal pulmonary embolism		N	2	Not recovered/Not resolved
	Paresthesia		N	1	Not recovered/Not resolved
	Insomnia		N	2	Not recovered/Not resolved
	Petechiae on lower legs		N	1	Not recovered/Not resolved
	Rash		N	1	Not recovered/Not resolved
	Scapular pain		N	1	Not recovered/Not resolved
	Dyspepsia		N	2	Not recovered/Not resolved
	Worsening of left pleural effusion		N	3	Recovered/Resolved
	Pruritus		N	1	Not recovered/Not resolved
	Hypomagnesemia				
	Sensory neuropathy		N	2	Recovered/Resolved
	Pruritus		N	1	Recovered/Resolved
	Weight gain		N	1	Not recovered/Not resolved
	Leukoencephalopathy		N	1	Not recovered/Not resolved
	Constipation		N	2	Not recovered/Not resolved
	Anorexia		N	2	Not recovered/Not resolved
	Adrenal insufficiency		N	1	Recovered/Resolved
	Lower limb weakness		N	2	Not recovered/Not resolved
	Immune effector cell-associated neurotoxicity syndrome (ICANS)		N	1	Recovered/Resolved
	Nausea		N	1	Not recovered/Not resolved
	ICANS		N	1	Not recovered/Not resolved
	Fever		N	1	Recovered/Resolved
	Cytokine release syndrome		N	1	Recovered/Resolved
	Hyperglycemia		N	3	Recovered/Resolved

Reviewer's comment: A total of 61 adverse events noted in the source records were not reported to the BLA. The majority of the AEs were Grade 1-2, with three Grade 3 events (hyperglycemia, pneumonitis, and pleural effusion), and two fatal events attributed to small cell lung cancer.

Dr. Ahn attributed the root cause of underreporting of AEs to lack of human resources to enter the data into the EDC in a timely manner.

The review of the sponsor's monitoring activities at Dr. Ahn's site showed serious deficiencies that impacted the quality of the data. The site monitors reportedly reviewed the eligibility criteria and adverse events but did not ensure that data was entered in the EDC. Only informed consent and drug administration were reviewed for all subjects.

On January 31, 2024, OSI, in conjunction with the review division, requested that Amgen provide a root-cause and impact analysis for the eligibility and AE discrepancies at Dr. Ahn's site, a summary of the data monitoring activities, and to perform a source record review of eligibility and adverse events for all subjects enrolled at all 5 sites in South Korea. Amgen's response to the information request was submitted on February 27, 2024 (BLA761344, supporting document 36).

Amgen stated that a source record review of all 5 sites in S. Korea identified a total of 109 previously unreported AEs among 27 subjects. The list of unreported AEs identified by Amgen at the S. Korean's sites are shown the Appendix, Table 2 of this document.

Twelve additional unreported AEs were found by Amgen at Dr. Ahn's site [identified as Study Specific Site Identification (SITEIDSS) (b) (4) by Amgen] in addition to the AEs identified during the FDA's inspection. These events are highlighted in the Table 2, Appendix. Five events identified by FDA during the inspection were not reported by Amgen: nausea (Subject (b) (6)), whole body pruritus (Subject (b) (6)), myalgia (Subject (b) (6)), anorexia (Subject (b) (6)), and hypomagnesemia (Subject (b) (6)).

Of the remaining 42 unreported AEs, (b) (4), 8 at Dr. Byoung Chul Cho's site (SITEIDSS (b) (4)).

Amgen stated that no additional eligibility deviations beyond those identified during the FDA inspection of Dr. Ahn were identified.

Based on the findings from the Sponsor's data review at the S. Korean sites, Amgen expanded source data verification to additional sites in Greece and has elected to further expand to conduct a 100% source data verification for all sites involved in Study 20200491. Upon completion, Amgen plans to submit an impact analysis of changes in the dataset on the benefit-risk profile of tarlatamab; updated data sets for Study 20200491, and revised tables, figures and listings (TFLs) for impacted data.

Please refer to Amgen's submission dated February 27, 2024, BLA761344, supporting document 36 for details of the Amgen's site monitoring and data quality control procedures.

Reviewer's comment: the large number of underreported AEs by the Korean sites, not captured during the Sponsor's monitoring activities is a major concern and put in question the integrity of the safety data submitted to support the approval of tarlatamab for the proposed indication. OSI agrees with Amgen's plan to conduct a 100% source data verification for all clinical sites involved in the Study 20200491 (DeLLphi-301).

2. Dr. Byoung Chul Cho (Site ID #25054)

50-1 Yonseiro, Seodaemun-Gu
Seoul, NA 3722,
South Korea

Inspection dates: January 29 – February 2, 2023

Dr. Cho was inspected as a routine PDUFA inspection for Study DeLLphi-301. Dr. Cho was previously inspected in May 2022.

At the time of the inspection, the site had screened 37 and enrolled 23 subjects in the study, of which 3 subjects were still on active treatment, 16 subjects were in follow-up phase and 4 subjects withdrew consent.

Source records for all 23 subjects were reviewed during the inspection and compared with data listings submitted to the BLA. Records reviewed included informed consent documents, eligibility criteria, adverse events reporting, protocol deviations, concomitant medications, laboratory results and investigational product administration.

Radiographic exams for tumor assessments were performed at the protocol specified timepoints and submitted for central review and assessment of efficacy endpoint.

Deficiencies in AE reporting were observed in 6 of the 23 subjects enrolled in the study. The majority of the missing AEs were mild in severity: grade 1 constipation, hiccup, sinus tachycardia, insomnia, sputum production, increased alanine aminotransferase, increased aspartate aminotransferase, fever, and increase creatinine, and grade 2 cancer pain. One subject (ID# [REDACTED] (b) (6)) with pre-existing hypertension, experienced a grade 3 hypertension and grade 2 headache 10 days after the last dose of tarlatamab. The event was reported as resolved with no action taken.

Reviewer's comment: the above missing AEs are not unexpected for the patients' underlying disease and treatment. None of the AEs were found to be significant for subject safety or for the reliability of the study data.

Amgen's review of the records identified 6 previously unreported AEs at Dr. Cho's site (identified as SITEIDSS (b) (4) by Amgen), of which, a grade 1 cytokine release syndrome was not previously identified during the FDA's inspection. Five events identified during the inspection were not reported by Amgen: grade 1 constipation, hiccup, sinus tachycardia, insomnia, sputum production.

Additional records reviewed during the inspection included, but were not limited to, IRB correspondence, staff training records, site monitoring reports, electronic records, and investigational product accountability. No regulatory violations or issues were observed.

Based on the results of the inspection, data generated at Dr. Cho's site appear acceptable in support of the proposed indication in the BLA.

3. Dr. Enriqueta Felip Font (Site ID #29404)

Passeig De La Vall D Hebron 119-129
Barcelona, NA 8035
Spain

Inspection dates: January 15 – 19, 2024

Dr. Font was inspected as a routine PDUFA inspection for Study DeLLphi-301. Dr. Font was previously inspected in November 2015 and April 2018.

At the time of the inspection, the site had screened 15 subjects and 14 had received study treatment. At the time of the data cut-off date, 7 subjects were on treatment, 3 subjects had died due to disease progression and 4 remained on follow-up phase. One additional subject was enrolled but did not receive study drug.

The inspection reviewed source records for 10 out of 14 subjects enrolled at the site. Documents reviewed included informed consent form for all subjects, inclusion and exclusion criteria, adverse events, treatment with the investigational product, protocol deviations, subject discontinuations, investigator RECIST assessment for the primary endpoint, and selected concomitant medications. Source records were compared with data listing submitted to the BLA.

Deficiencies in AE reporting were observed in 3 out of 14 subjects enrolled at the site. The unreported AEs were mild in severity and expected for the underlying disease: upper respiratory tract infection (Grade 2), right cervical edema (Grade 1), hand pruritis (Grade 1) and decreased TSH (Grade 1). None of the missing data was found to be significant for subject safety or for the reliability of the study data.

Tumor assessments for the primary efficacy endpoint of ORR were performed according to the protocol and all scans were submitted to the imaging CRO for central

assessment. The inspection reviewed the tumor response assessments by the investigator and found no discrepancies when compared with the listing submitted to the BLA.

Additional documents reviewed during the inspection included, but were not limited to, local Ethics Committee approvals, communication with the sponsor, monitoring activities, CI and co-investigator's financial disclosures, and investigational drug accountability.

Based on the results of the inspection, the DeLLphi-301 study data generated at Dr. Font's site appear acceptable in support of the proposed indication in the BLA.

4.

(b) (4)

(b) (4) was inspected as a routine PDUFA inspection for Study DeLLphi-301. The firm was previously inspected in (b) (4).

This inspection reviewed (b) (4) responsibilities to perform an independent central imaging review for Study DeLLphi-301. Records reviewed included Independent Review Charters, communication between the Sponsor, Amgen, Inc. and (b) (4) readers qualifications and training, standard operating procedures, financial disclosure forms, and electronic databases. (b) (4) data collection and handling procedures, readers' adherence to the review charter, and readers blinding and adjudication procedures were also reviewed and found to be adequate.

Source records for 30 subjects selected at random were verified and compared with the data listing provided by the Sponsor to the FDA. The inspection verified the baseline scan dates, tumor assessments at various follow-up time points for Readers 1 and Reader 2, adjudication assessment, best overall response, and tumor measurements. No discrepancies were observed.

The ID of the subjects whose tumor measurements were verified are listed in the following table:

Subject ID #	(b) (6)
(b) (6)	

(b) (4) procedures in performing image analysis, compliance with the Imaging Review Charter, and appropriate regulations appeared adequate.

Based on the results of the inspection, the imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the BLA.

CONCURRENCE:

{See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DARRTS: BLA761344
Review Division /Project Manager/Ashley Lane
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

APPENDIX

Table 2. List of Unreported AEs Identified by Amgen
(SITEIDSS # (b) (4))

Site ID	Subject	Preferred term	AE start date	Grade	AE outcome
(b) (4)	(b) (6)	Pleural effusion	(b) (6)	2	Recovered/Resolved
		Anemia		2	Recovered/Resolved
		Pruritus		1	Not Recovered/Not Resolved
		Myalgia		1	Not Recovered/Not Resolved
		Hypothyroidism		2	Not Recovered/Not Resolved
		Arthralgia		1	Not Recovered/Not Resolved
		Cytokine release syndrome		1	Not Recovered/Not Resolved
		Hyponatremia		2	Not Recovered/Not Resolved
		Vomiting		1	
		Hypocalcemia		2	Recovered/Resolved
		Cytokine release syndrome		1	Recovered/Resolved
		Hypoalbuminemia		2	Recovered/Resolved
		Hypophosphatemia		2	Recovered/Resolved
		Small cell lung cancer		5	FATAL
		Hypertension		3	Recovered/Resolved
		Pneumonitis		3	Not Recovered/Not Resolved
		Oral candidiasis		2	Recovered/Resolved
		Small cell lung cancer		5	FATAL
		Nausea		1	Recovered/Resolved
		Nausea		2	Recovered/Resolved
		Myalgia		1	Recovered/Resolved
		Nausea		2	Recovered/Resolved
		Pyrexia		1	Recovered/Resolved
		Arthralgia		2	Recovered/Resolved
		Stomatitis		1	Recovered/Resolved
		Pulmonary embolism		2	Not Recovered/Not Resolved
		Herpes zoster		2	Recovered/Resolved
		Dyslipidemia		1	Not Recovered/Not Resolved
		Hemoptysis		2	Recovered/Resolved
		Pneumonia viral		2	Recovered/Resolved
		Constipation		2	Not Recovered/Not Resolved
		Hypothyroidism		1	
		Aspartate aminotransferase increased		2	Recovered/Resolved
		Alanine aminotransferase increased		2	Recovered/Resolved
		Infusion related reaction		2	Recovered/Resolved
		Nausea		1	Not Recovered/Not Resolved

(b) (4)	(b) (6)	Embolism	(b) (6)	2	Not Recovered/Not Resolved
		Paresthesia		1	Not Recovered/Not Resolved
		Insomnia		2	Not Recovered/Not Resolved
		Petechiae		1	Not Recovered/Not Resolved
		Rash		1	Not Recovered/Not Resolved
		Dyspepsia		2	Not Recovered/Not Resolved
		Musculoskeletal pain		1	Not Recovered/Not Resolved
		Pleural effusion		3	Recovered/Resolved
		Non-cardiac chest pain*		1	Not Recovered/Not Resolved
		Pruritus		1	Not Recovered/Not Resolved
		Electrolyte imbalance*		2	Recovered/Resolved
		Peripheral sensory neuropathy		2	Recovered/Resolved
		Pruritus		1	Recovered/Resolved
		Weight increased		1	Not Recovered/Not Resolved
		Leukoencephalopathy		1	Not Recovered/Not Resolved
		Constipation		2	Not Recovered/Not Resolved
		Decreased appetite		2	Not Recovered/Not Resolved
		Adrenal insufficiency		1	Recovered/Resolved
		Adrenal insufficiency*		2	Not Recovered/Not Resolved
		Muscular weakness		2	Not Recovered/Not Resolved
		Tooth loss*		2	
		Hypothyroidism*		2	Not Recovered/Not Resolved
		Pericardial effusion*		2	Not Recovered/Not Resolved
		Nausea		1	Not Recovered/Not Resolved
		Immune effector cell-associated neurotoxicity syndrome		1	Recovered/Resolved
		Fatigue*		1	Recovered/Resolved
		Immune effector cell-associated neurotoxicity syndrome		1	Not Recovered/Not Resolved
		Pyrexia		1	Recovered/Resolved
		Cytokine release syndrome		1	Recovered/Resolved
		Hyperglycemia		3	Recovered/Resolved
		Limb mass*		1	Not Recovered/Not Resolved
		Aspartate aminotransferase increased		1	Not Recovered/Not Resolved
		Cancer pain		2	Not Recovered/Not Resolved
		Alanine aminotransferase increased		1	Not Recovered/Not Resolved
	Pyrexia		1	Recovered/Resolved	
	Cytokine release syndrome		1	Recovered/Resolved	
	Headache		2	Recovered/Resolved	

(b) (4)	(b) (6)	(b) (6)	
	Hypertension	3	Recovered/Resolved
	Blood creatinine increased	1	Not Recovered/Not Resolved
	Dysuria	1	Recovered/Resolved
	Fatigue	2	Recovered/Resolved
	Decreased appetite	1	Recovered/Resolved
	Flushing	1	Recovered/Resolved
	Fatigue	2	Not Recovered/Not Resolved
	Decreased appetite	2	Recovered/Resolved
	Constipation	2	Not Recovered/Not Resolved
	Insomnia	2	Recovered/Resolved
	Decreased appetite	2	Not Recovered/Not Resolved
	Nausea	2	Recovered/Resolved
	Decreased appetite	2	Recovered/Resolved
	White blood cell count decreased	2	Recovered/Resolved
	Neutrophil count decreased	2	Recovered/Resolved
	Hypomagnesaemia	1	Recovered/Resolved
	Breast swelling	1	Not Recovered/Not Resolved
	White blood cell count decreased	3	Recovered/Resolved
	Neutrophil count decreased	3	Recovered/Resolved
	White blood cell count decreased	2	Recovered/Resolved
	Neutrophil count decreased	2	Recovered/Resolved
	Arthralgia	1	Not Recovered/Not Resolved
	Insomnia	1	Recovered/Resolved
	COVID-19	2	Recovered/Resolved
	Neutrophil count decreased	2	Recovered/Resolved
	White blood cell count decreased	2	Recovered/Resolved
	Neuropathy peripheral	1	Recovered/Resolved
	White blood cell count decreased	2	Recovered/Resolved
	Neuropathy peripheral	1	Not Recovered/Not Resolved
	Blood creatinine increased	1	Recovered/Resolved
	Blood bilirubin increased	1	Recovered/Resolved
	Decreased appetite	2	Recovered/Resolved
	Blood follicle stimulating hormone increased	1	Not Recovered/Not Resolved
	COVID-19	1	Recovered/Resolved
	Weight decreased	2	Not Recovered/Not Resolved
	Bladder dysfunction	2	Recovered/Resolved

**Unreported AEs found at Dr. Ahn's site by Amgen, in addition to those identified during FDA's inspection*

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/s/

LEE HONG PAI SCHERF
03/26/2024 04:16:28 PM

MICHELE B FEDOWITZ
03/26/2024 08:49:50 PM

JENN W SELLERS
03/26/2024 09:04:05 PM

HUMAN FACTORS STUDY REPORT AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	03/06/2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761344
Product Type:	Single Ingredient Product
Product, Name, Dosage Form and Strength:	Imdelltra (tarlatamab-xxxx) ^a for injection, 1 mg/vial and 10 mg/vial
Rx or OTC:	Prescription (Rx)
Applicant Name:	Amgen Inc.
FDA Received Date:	10/12/2023, 01/02/2024, 01/11/2024
TTT ID #:	2023-6728, 2023-6460
DMEPA 2 Safety Evaluator:	Farinaz Beniesfahany, PharmD
DMEPA 2 Team Leader:	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Deputy Director	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761344 for Imdelltra (tarlatamab-xxxx) for injection.

1.1 PRODUCT INFORMATION

^a The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder tarlatamab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

Table 1 presents relevant product information for Imdelltra that Amgen Inc. submitted on 10/12/2023.

Table 1. Relevant Product Information for Imdelltra	
Initial Approval Date	N/A
Active Ingredient	tarlatamab-xxxx
Indication	Indicated for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy
Route of Administration	Intravenous infusion
Dosage Form	For injection
Strength	1 mg/vial and 10 mg/vial
Dose and Frequency	1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter. Treat patients until disease progression or unacceptable toxicity.
How Supplied	Sterile, preservative free white to slightly yellow, lyophilized powder supplied as follows: • 1 mg package (NDC 55513-059-01) includes 1 single-dose vial of 1 mg IMDELLTRA and 2 vials of 7 mL Intravenous Solution Stabilizer (IVSS). • 10 mg package (NDC 55513-077-01) contains 1 single dose vial of 10 mg IMDELLTRA and 2 vials of 7 mL IVSS.
Storage	Store IMDELLTRA and IVSS vials in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze. Store lyophilized IMDELLTRA and IVSS vials for a maximum of 24 hours at room temperature [23°C to 25°C (73°F to 77°F)] in the original carton to protect from light.
Intended Users	Pharmacists, pharmacy technicians
Intended Use Environment	Hospital pharmacy
Other important HF-related information relevant for this review	Based on the use-related risk assessment, the Applicant determined that a HF validation study was needed to demonstrate safe and effective use of the proposed product. Of note, we are aware of currently marketed products that also utilize IVSS in its preparation.

1.2 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On December 18, 2023, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the term BLA 761344. The identified reviews and FDA/Applicant interactions are provided below.

- On 5/18/2023, we issued an Information Request (IR) to request the Applicant to perform a proactive risk assessment to identify the risk for medication errors that may occur due to inclusion of the IVSS in the proposed packaging configuration and determine whether or not a HF validation study should be conducted. On 5/24/2023, the Applicant responded stating that “Amgen intends to provide the results of the HF Validation Study as part of the BLA 761344 submission”.
- DMEPA did not previously review the HF validation study protocol prior to the commencement of the HF validation study.
- On 10/12/2023, the Applicant submitted the results of the HF validation study under BLA 761344, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product information	Section 1.1
Background Information Previous DMEPA HF Reviews	Section 1.2
Human Factors (HF) Validation Study Report and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Labels and Labeling	Appendix C

2 OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

The sections below provide a summary of the study design, and our evaluation of the study methodology to determine if the study has been appropriately designed to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study design. See Appendix A for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	Pharmacist (n=15)
Training	None
Test Environment	Similar to a pharmacy setting with stations that mimic a buffer room for donning PPE and a clean room with representative flow hood to mimic admixing
Materials	• 1 package containing 1 vial of lyophilized placebo representing 1 mg or 10 mg of the Imdelltra, 2 vials of 10 mL intravenous solution stabilizer, 1 Prescribing Information (PI), and 1 Medication guide • syringes of various sizes (1 mL, 3 mL, 5 mL, 10 mL, 20 mL, and 50 mL) • needles: 18 to 23 gauge (for manipulation of vial) • sterile preservative-free water for injection (sWFI) • 250 mL infusion bags prefilled with 0.9% Sodium Chloride Injection, USP • Intravenous (IV) tubing • Sharps containers (big and small) • Hair net • Gowns • Safety glasses • Gloves • Alcohol wipes
Sequence of Study	• Introduction • Initial interview • Session information • Simulated-use dose scenario (1 mg or 10 mg counterbalanced between participants) • Dose scenario debrief and root cause analysis • Comprehension questions • Comprehension questions debrief and root cause analysis • Final thoughts/wrap up

2.2 DISCUSSION OF METHODOLOGY

Per the Applicant's use-related risk analysis (URRA), pharmacy technicians are intended users of the proposed product; however, they were not included in the HF validation study. The Applicant states,

Although both pharmacists and pharmacy technicians are involved with preparing the drug product solution to the prescribed dose ... pharmacists have the sole responsibility of determining how their pharmacy would prepare a drug based off their interpretation of the drug product PI. The pharmacy technician is under the pharmacist's supervision and follows instructions ... that are developed by pharmacists and does not perform the task of interpreting information from the PI into steps that need to be followed.

We considered the Applicant's justification for not including pharmacy technicians in the HF validation study and we disagree because we consider pharmacists and pharmacy technicians to be distinct user groups due to differences in professional experience, knowledge, and expertise. However, this methodology limitation does not preclude our review of the HF validation study results in this particular instance.

3 RESULTS AND ANALYSIS

In this section, we have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), the Applicant's URRA, the participants' subjective feedback, the Applicant's RCA, and the Applicant's comments and proposed mitigations (if applicable) to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product.

The HF validation study results showed issue with the following simulated-use task:

(b) (4)

We considered the participant's subjective feedback, the Applicant's URRA, RCA, our evaluation of the overall residual risks, the implementation of best practice standards and the Applicant's proposed mitigations (including any post-HFVS changes to the user interface). As a result, in this particular instance we find the proposed user interface has been appropriately designed and we did not identify recommendations to address the identified issue with the above task.

In Table 4 below, we provide a summary of the use-related events supplied by the Applicant along with our detailed analysis of use-related events that resulted in recommendations and document our points of dissent with the Applicant's findings.

Table 4. Focused Analysis of Reported Issues and DMEPA's Recommendations

Summary of Information Supplied by Applicant			DMEPA's Identified Areas of Dissent and Recommendations								
<u>Task</u>: inject sWFI into drug product vial <u>Scenario</u>: simulated use <table><tr><td>Reported Issues:</td><td>Participant Type(s):</td></tr><tr><td>UE (n=1)</td><td>Pharmacist (n=1)</td></tr><tr><td>CC (n=0)</td><td></td></tr><tr><td>UD (n=0)</td><td></td></tr></table>			Reported Issues:	Participant Type(s):	UE (n=1)	Pharmacist (n=1)	CC (n=0)		UD (n=0)		
Reported Issues:	Participant Type(s):										
UE (n=1)	Pharmacist (n=1)										
CC (n=0)											
UD (n=0)											
Observed event: Did not inject the sWFI onto the walls, and instead injected straight down into the vial											
Relevant RCA/Subjective Feedback: Information not salient: Information relating to directing the sWFI to the walls of the vial is not salient in Section 2 of the PI.											
Based on the Applicant's URRRA, performing this task incorrectly or not at all may result in: - Underdose-decreased efficacy - Overdose- Grade 1-4 drug related adverse reaction - Compromised prepared product- Grade 1-4 drug related adverse reaction											
Applicant's Comments and Proposed Post- HFVS Mitigations: The Applicant determined that no additional changes to the user interface are needed to further address the reported issue for this task.			The PI statement (b) (4) is immediately after the statement describing the (b) (4) concentration and lacks prominence. Therefore, we find that Section 2 of the PI can be improved to make the instructions regarding the proper technique for directing the sWFI to the walls of the vial to minimize foaming more prominent. We provide our recommendation below in								

	Table 5. This recommendation can be implemented without the submission of additional HF data.								
<u>Task:</u> withdraw correct volume of reconstituted drug product from vial and inject into IV bag <u>Scenario:</u> simulated use <table> <tr> <td>Reported Issues:</td><td>Participant Type(s):</td></tr> <tr> <td>UE (n=2)</td><td>Pharmacist (n=2)</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Reported Issues:	Participant Type(s):	UE (n=2)	Pharmacist (n=2)	CC (n=0)		UD (n=0)		
Reported Issues:	Participant Type(s):								
UE (n=2)	Pharmacist (n=2)								
CC (n=0)									
UD (n=0)									
Observed events: Both participants were assigned to the 10 mg dose scenario and incorrectly transferred 4.4 mL of reconstituted drug instead of 4.2 mL.									
Relevant RCA/Subjective Feedback: - Information not salient: Information related to the required amount of reconstituted drug was not salient in the PI. - PI content clarity: Table 3 of the PI did not clearly communicate that the amount of sWFI added to the vial was not the same as the amount of reconstituted drug product to be added to the IV bag.									
Based on the Applicant's URRAs, performing this task incorrectly or not at all may result in: - Underdose-decreased efficacy - Overdose- Grade 1-4 drug related adverse reaction									
Applicant's Comments and Proposed Post- HFVS Mitigations: The Applicant determined that no additional changes to the user interface are needed to further address the reported issues for this task.	We find the footnote of Table 5 (i.e., (b) (4)) can be improved to mention the volume of reconstituted drug product that needs to be added to the IV bag. Additionally, the information regarding the required volume of Imdelltra to add to the IV bag can be improved to include this information in tabular format under the applicable PI section/task. We provide our recommendation								

			below in Table 5. This recommendation can be implemented without the submission of additional HF data.
<u>Task:</u> remove air from IV bag <u>Scenario:</u> simulated use			
	Reported Issues:	Participant Type(s):	
	UE (n=2)	Pharmacist (n=2)	
	CC (n=0)		
	UD (n=1)	Pharmacist (n=1)	
Observed events: - Participant was unsure on how to remove air from the IV bag. They initially attempted to use the IV tubing to remove the air but eventually used a syringe to remove air from the IV bag. - Did not remove air from the IV bag			
Relevant RCA/Subjective Feedback: The PI does not provide information on how to remove the air from the IV bag.			
Based on the Applicant's URRAs, performing this task incorrectly or not at all may result in: Underdose- decreased efficacy			
Applicant's Comments and Proposed Post- HFVS Mitigations: The Applicant determined that no additional changes to the user interface are needed to further address the reported issues for this task.			
Task: store prepared Imdelltra IV bag Scenario: Comprehension			
	Reported Issues:	Participant Type(s):	
	UE (n=1)	Pharmacist (n=1)	
	CC (n=0)		
	UD (n=0)		

Observed event: Did not understand that the storage time provided in the PI includes the infusion time (correctly identified that the prepared IV bag could be stored for 8 hours, but did not understand the 8 hours includes the infusion time)	
Relevant RCA/Subjective Feedback: Information not salient: The information indicating that the total storage time included the infusion time was not salient in the PI.	
Based on the Applicant's URRAs, performing this task incorrectly or not at all may result in: Degraded drug product use- decreased efficacy	
Applicant's Comments and Proposed Post- HFVS Mitigations: In response to the use error, the Applicant implemented the following post-validation revision: "Update to PI: addition of asterisk to first column of "Maximum Storage Time" in Table 6 to call out footnote." The Applicant did not validate this revision.	We determined the Applicant's proposed mitigation does not adequately address user performance on comprehension of the task of storing a prepared Imdelltra IV bag. Specifically, we find the statements intended to clarify the storage time of the prepared Imdelltra IV bag includes the duration of the infusion can be further improved and be more prominent. We provide our recommendation below in Table 5. This recommendation can be implemented without the submission of additional HF data.

4 LABELS AND LABELING

Tables 5 and 6 below include the identified medication error issues with the submitted labels and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2.3 of your prescribing information (PI) includes (b) (4)	(b) (4)	We recommend removing the aforementioned (b) (4) from Section 2.3 of the PI.
2.	Section 2.3 of the PI can be improved to present the preparation instructions in a stepwise manner.	The current formatting is not conducive to readability or easily identifying key information.	We recommend revising Section 2.3 of the PI to present the preparation instructions in a stepwise manner. For example: Step 1: “Reconstitute IMDELLTRA with ...” Step 2: “Withdraw 0.9% Sodium ...” Step 3: “Add IV Solution Stabilizer ...” Step 4: “Add Reconstituted IMDELLTRA” Step 5: “Remove air ...”
3.	The use of term (b) (4) in Section 2.3.4 is inaccurate as the product requires	Inclusion of inaccurate statements may lead to wrong technique preparation medication errors.	We recommend replacing the term (b) (4) with “Resulting concentration” in Section 2.3.4.

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	further dilution following reconstitution.		
4.	The following statement is repeated twice in Section 2.3.4: “Reconstitute IMDELLTRA with Sterile Water for Injection, (b) (4)	Redundancy may affect the readability of the important information which may lead to confusion or product preparation medication errors.	We recommend removing the presentation of the aforementioned statement that includes (b) (4) 2.3.4.
5.	The following statement in Section 2.3.8 can be improved to clarify that (b) (4)	Unclear instructions can result in confusion and wrong technique preparation medication errors.	Revise the aforementioned statement to “the final concentrations for the different strength vials are NOT the same following reconstitution and further dilution”.
6.	In the HF validation study, the subjective feedback and RCA indicated that a participant injected the SWFI directly onto the lyophilized powder instead of onto the walls of the drug product vial because the instructions were not salient. This refers to the proposed PI Section 2.3.4.	Based on the URRA, failure to inject SWFI onto the walls of the drug product vial can result in decreased efficacy due to underdose or Grade 1-4 drug related adverse reactions due to overdose or compromised prepared product.	We recommend in Section 2.3.4, increasing the prominence of the instruction (b) (4) by rewording and making it a separate substep. Additionally, we recommend revising the step (b) (4) and relocate this information to appear before Table 5. Refer to row #16 below for our recommendations for Section 2.3.4.
7.	In the tables presented in Section 2.3, the units of measure (i.e., mg, mL,	Including units of measurement with each numerical unit will help	We recommend including units of measurement (i.e., mg, mL, or mg/mL) with each numerical unit in the rows.

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION									
	mg/mL) are located within the header of the rows instead of next to the corresponding numerical unit in each row.	mitigate potential medication dosing errors.										
8.	In the HF validation study, there were subjective feedback and RCA that indicate the information related to the required amount of reconstituted drug was not salient in the PI. This refers to the proposed PI Sections 2.3.4 and 2.3.8.	Based on the URRRA, failure to perform the task of “withdraw correct volume of reconstituted drug product from vial and inject into IV bag” can result in decreased efficacy due to underdose and Grade 1-4 drug related adverse reaction due to overdose.	We recommend revising the footnote for Table 5 in Section 2.3.4 from (b) (4) to “Each vial contains overfill to allow for withdrawal of 1.1 mL (1 mg vial) or 4.2 mL (10 mg vial) after reconstitution.” We also recommend revising Section 2.3.8 to include the following new table under the statement “NOTE: the final concentrations ...” Table XX. Required Amount of Reconstituted IMDELLTRA to Add to 250 mL IV Bag <table><tr><th>IMDELLTRA Vial Strength</th><th>IMDELLTRA Dose</th><th>Volume of Reconstituted IMDELLTRA to Add to 250 mL IV Bag</th></tr><tr><td>1 mg</td><td>1 mg</td><td>1.1 mL</td></tr><tr><td>10 mg</td><td>10 mg</td><td>4.2 mL</td></tr></table>	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
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										
9.	In the HF validation study, a participant was unsure on how to remove air from the IV bag. Subjective feedback and your RCA indicate that information regarding how to remove air from IV bag is not provided in the PI.	Per URRRA, failure to perform the task of “remove air from IV bag” can result in decreased efficacy due to underdose.	Revise Section 2.3.9 to include instructions regarding the proper technique to remove air from the IV bag. For example and if accurate, revise the statement “Remove air from...” to “Remove air from the IV bag with an empty syringe...”).									

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
10.	The statement “Remove air from the IV bag” presented in (b) (4)	Difficulty with reading instructions and redundancy may lead to confusion or product preparation medication errors.	Remove (b) (4) from Section 2.3.9.
11.	Section 2.3.9 can be improved to emphasize the importance of removing air from the IV bag prior to administration.	The practice of removing air from an IV bag may not be standard practice; therefore, we are concerned that users may not understand the impact/importance of performing this task without additional information.	We recommend adding information regarding the purpose of air removal from IV bag (i.e., to avoid foaming) under Section 2.3.9. For example, consider to revise the statement “Remove air from...” to “Remove air from the IV bag with an empty syringe to avoid foaming regardless of...”.
12.	The instructions for priming the IV tubing lacks prominence because they are presented under Section “2.3.9 (b) (4) In addition, the following statement under Section 2.3.9 can be improved to clarify the word (b) (4)	Important priming information may be overlooked or misunderstood resulting in wrong technique medication errors.	We recommend revising Section 2.3 to present IV tubing priming instructions as a separate step. For example: • Step 6: Prime IV tubing In addition, consider revising the priming instructions to the following: “Prime the IV tubing with either 0.9% Sodium Chloride for Injection or with the final prepared product.”

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION																		
13.	Section 2 can be improved to include the information provided in (b) (4) (b) (4)	The current formatting is not conducive to readability or easily identifying key information. In addition, redundant information may lead to important preparation instructions being overlooked resulting in wrong preparation medication errors.	We recommend relocating the applicable information (b) (4) to the corresponding sections and remove the corresponding note (b) (4). For example: - Include the following table in Section 2.3.6: Table XX. Required Amount of 0.9% Sodium Chloride to Withdraw from 250 mL IV Bag <table><tr><th>IMDELLTR A Vial Strength</th><th>IMDELLTRA Dose</th><th>Volume of 0.9% Sodium Chloride to Withdraw From 250 mL IV Bag</th></tr><tr><td>1 mg</td><td>1 mg</td><td>14 mL</td></tr><tr><td>10 mg</td><td>10 mg</td><td>17 mL</td></tr></table> - Include the following table in Section 2.3.7: Table XX. Required Amount of IV Solution Stabilizer (IVSS) to Add to IV Bag <table><tr><th>IMDELLTR A Vial Strength</th><th>IMDELLTRA Dose</th><th>Volume of IV Solution Stabilizer (IVSS) to Add to IV Bag</th></tr><tr><td>1 mg</td><td>1 mg</td><td>13 mL</td></tr><tr><td>10 mg</td><td>10 mg</td><td>13 mL</td></tr></table>	IMDELLTR A 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	IMDELLTR A 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
IMDELLTR A 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																			
IMDELLTR A 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																			
14.	The route of administration is abbreviated as “IV”.	Presenting the route of administration as an abbreviation may lead to misinterpretation of the intended route of administration.	We recommend revising “IV” to “Intravenous”.																		
15.	In the HF validation study, there were subjective feedback and RCA that	Per URRRA, failure to perform the task of (b) (4)	Revise Section 2.4.2 to include the following statement before Table 8:																		

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	suggest the storage information for a prepared Imdelltra IV bag (i.e., the total storage time includes the infusion time) was not salient in the PI.	can result in decreased efficacy due to degraded drug product use.	(b) (4) In addition, increase the prominence of the discard statement (i.e., (b) (4) in the footnote for Table 8 by relocating it to appear as a separate statement outside of the footnote and revising to read: (b) (4)

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
16.	Recommendations for Section 2.3.4 are noted in track changes below: (b) (4)		
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	A description of the dosage form is not provided (e.g., color of lyophilized powder).	A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(4)(ii).	Provide a description of identifying characteristics of the dosage form in accordance with 21 CFR 201.57(c)(4)(ii).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As proposed, Section 16 presents the dosage form incorrectly as (b) (4)	The correct dosage form that is consistent with USP requirements (i.e.,	Revise the dosage form to “for injection” in Section 16.

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		“for injection”) needs to be presented consistently throughout the labels and labeling.	
2.	The statement (b) (4) can be improved to clarify that storing the product at room temperature is an alternate storage method.	Unclear storage instructions can result in deteriorated drug medication errors.	Revise the aforementioned statement to “IMDELLTRA and IV Solution Stabilizer (IVSS) vials may be stored at room temperature [23°C to 25°C (73°F to 77°F)] for up to 24 hours in the original carton to protect from light.”

Table 6. Identified Issues and Recommendations for Amgen Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Comments (All Container Labels and Carton Labeling)			
1.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space

Table 6. Identified Issues and Recommendations for Amgen Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			limitations on the drug package, the human readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends a hyphen or forward slash to separate the portions of the expiration date. See <i>Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)</i> .
Imdelltra Container Labels and Carton Labeling			
1.	The design and color of letter (b) (4) in the proprietary name (b) (4)	The lack of prominence of the letter (b) (4) in the proprietary name impacts the interpretation and the readability of the proprietary name.	Revise the appearance of the proprietary name such that the letter (b) (4) appears in the same color as the other letters in the proprietary name "IMDELLTRA". Once in the same color, consider if the (b) (4) still interferes with the interpretation and readability of the name and if so, remove the (b) (4)
2.	The strength lacks adequate spacing between the numerical dose and unit of measure.	Lack of adequate spacing may impact readability and might result in wrong strength errors. For example (e.g., the "m" in mg can sometimes be mistaken as a zero or two zeros).	We recommend placing adequate space between the numerical dose and unit of measure (e.g., [10 mg instead of 10mg]) to improve readability.
3.	The 1 mg and 10 mg strengths are not clearly differentiated because the (b) (4) colors overlap with the font colors used for the	Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most	We recommend revising the color scheme of the 1 mg and 10 mg strengths such that the strengths appear in their own unique color and (b) (4)

Table 6. Identified Issues and Recommendations for Amgen Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	proprietary name, proper name, and dosage form.	effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme.	
4.	The storage statements are inconsistent with the storage information in the Prescribing Information (PI). For example, information regarding storing in the carton is missing on the medication container labels and the statement (b) (4) presented on the carton labeling is not present in Section 16 of the PI.	Inconsistency between the storage statements may lead to confusion and deteriorated drug medication errors.	Revise the storage statement on the carton labeling (b) (4) labels (if space permits) to consistently state, "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze."
Imdelltra Container Labels			
1.	As currently presented, the statement "Store at 2°C to 8°C (36°F to 46°F)." competes in prominence with the proper name, the strength statement under dosage form (i.e., for injection) and route of administration on the principal display panel (PDP).	The critical product information (e.g., proprietary name, proper name, product strength, route of administration, etc.) should be the most prominent information on the PDP.	Decrease the prominence of the statement "Store at 2°C to 8°C (36°F to 46°F)."
2.	The "Rx only" statement on the 1 mg strength medication container label appears more prominent than other	The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel.	We recommend the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. <i>See Guidance for Industry: Safety Considerations for Container</i>

Table 6. Identified Issues and Recommendations for Amgen Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	critical information (e.g., strength) on the principal display panel.		<i>Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).</i>
Carton Labeling			
1.	As currently presented, there are no instructions on the PDP to indicate that the product must be reconstituted and further diluted for intravenous infusion.	This lack of information may lead to wrong preparation errors.	We recommend including a statement on the principal display panel to indicate that the product must be reconstituted and further diluted prior to administration. For example, "Must be reconstituted with sterile water for injection and further diluted."
2.	The term (b) (4) in the following statement is unclear: (b) (4)	Unclear terminology can lead to confusion.	Replace the term (b) (4) with its intended meaning. (e.g., proprietary name, proper name, etc.)
3.	The machine-readable product identifier appears to be missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a	The DSCSA guidance recommends the machine-readable (i.e., 2D data matrix barcode) be located near the human readable portion below: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date] We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-

Table 6. Identified Issues and Recommendations for Amgen Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		human-readable form and machine-readable (2D data matrix barcode) format.	gen/documents/document/ucm621044.pdf . ^b
Intravenous Solution Stabilizer (IVSS) Container Label			
1.	The warning statement (b) (4) may be further improved.	Post-marketing reports have shown that negative statements may have the opposite of the intended meaning because the word (b) (4) can be overlooked and misinterpreted as an affirmative action.	Revise to “Use ONLY to prepare the infusion bag prior to adding reconstituted IMDELLTRA.” If space allows, after the “Use ONLY...” add “DO NOT use IV Solution Stabilizer to reconstitute Imdeelltra”.
Carton Labeling and IVSS Container Label			
1.	As currently presented, the proprietary name is denoted by the placeholder “Tradename”.	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our 07/05/2023 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Imdeelltra, was found conditionally acceptable. We recommend replacing the placeholder “Tradename” with the conditionally acceptable proprietary name, Imdeelltra, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
Imdeelltra Container Labels and IVSS Container Label			
1.	As currently presented, the package type term, single-dose vial and the discard statement “Discard unused portion”,	Consistent use of the correct package type term will promote proper use of the drug product. The lack of this information may	Add the statement, “Single-Dose Vial. Discard Unused Portion” to the PDP. <i>See Guidance for Industry: Selection of the Appropriate Package Type Terms and</i>

^b When final, this guidance will represent FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>

Table 6. Identified Issues and Recommendations for Amgen Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	is not stated on the principal display panel (PDP) of the container labels for both the medication vial and IVSS vial.	lead to wrong technique medication errors during preparation of the product. In addition, Inclusion of the discard statement helps minimize the risk of the entire contents of the vial being given as a single dose.	<i>Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018).</i>

5 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table 5 for the Division. These changes can be implemented without submitting additional HF validation testing data for Agency review.

Additionally, our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 5 for the Division and in Table 6 for the Applicant. We ask that the Division convey Table 6 in its entirety to the Applicant so that recommendations are implemented for this BLA 761344. These changes can be implemented without submitting additional HF validation testing results for Agency review.

6 APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

- The HF study results report and background information can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761344\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\scl\5354-other-stud-rep\585521\585521.pdf>
- The use-related risk analysis can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761344\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\scl\5354-other-stud-rep\583826\583826.pdf>

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 12/19/2023, we issued an Information Request (IR) to request the Applicant to provide their human factors validation study protocol. On 1/2/2024, the Applicant did provide an acceptable response that can be accessed in EDR via:

<\\CDSESUB1\EVSPROD\bla761344\0018\m1\us\111-information-amendment\response-to-fda-information-request-received-19-december.pdf>

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error experiences with similar products, we reviewed the following Imdelltra labels and labeling submitted by Amgen Inc.

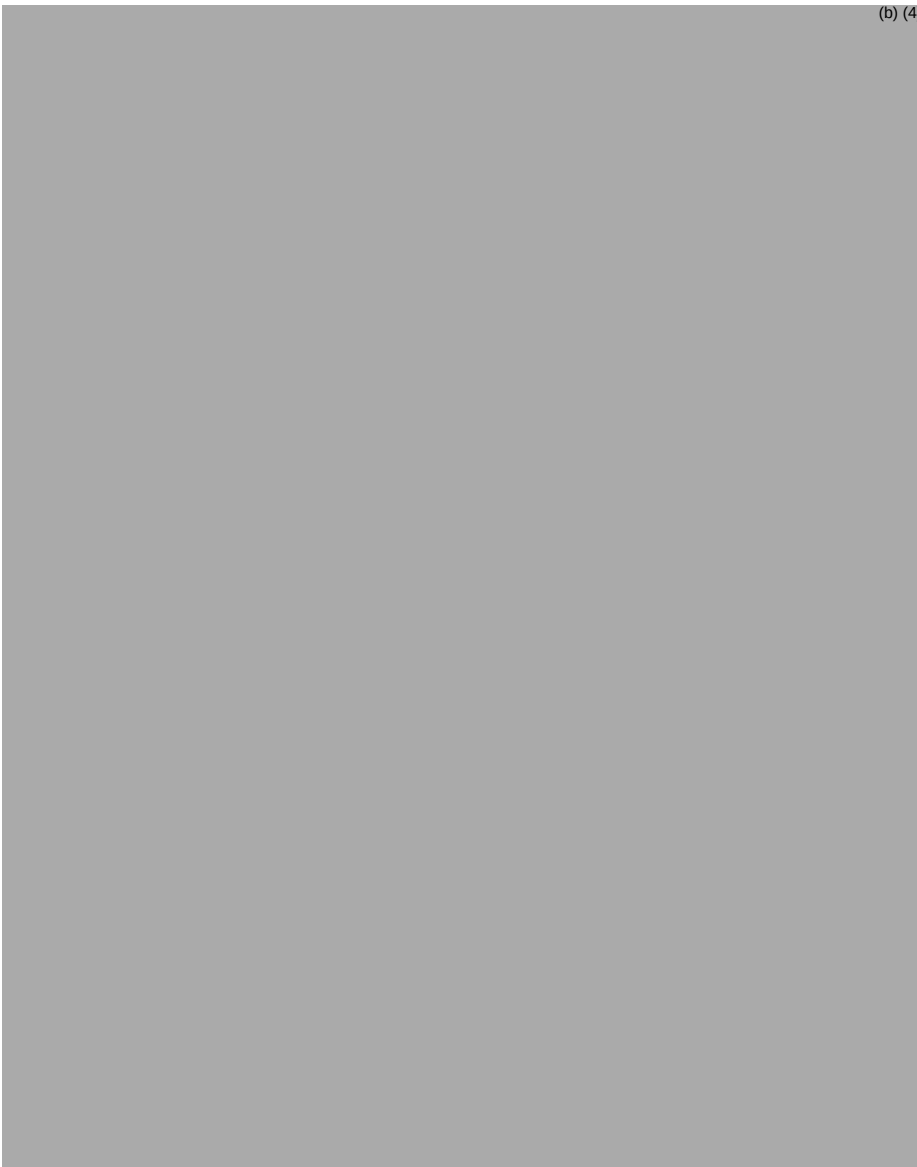
- Container labels received on 10/12/2023
- Carton labeling received on 10/12/2023
- Patient information (Image not shown) received on 10/12/2023 available from <\\CDSESUB1\EVSPROD\bla761344\0007\m1\us\114-labeling\draft\labeling\d-imdelltra-us-ppi-initial-c-2023-1003.pdf>

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Prescribing Information (Image not shown), Received on 01/11/2024 available from <\\CDSESUB1\EVSPROD\bla761344\0020\m1\us\114-labeling\draft\labeling\d-imdelltra-uspi-initial-c-2023-1003.pdf>

D.2 Label and Labeling Images

Container labels



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FARINAZ BENIESFAHANY
03/06/2024 03:48:43 PM

COLLEEN L LITTLE
03/06/2024 04:01:23 PM

COLLEEN L LITTLE on behalf of LOLITA G STERRETT
03/06/2024 04:02:06 PM

CHI-MING TU
03/06/2024 04:42:47 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 8, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Ashley Lane
DO2

Subject: QT Consult to BLA 761344 (SDN 008)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/15/2023 regarding the Review Division's QT related question. We reviewed the following materials:

- Summary of Clinical Pharmacology studies ([BLA761344 / SDN 8](#));
- Clinical Study Report for study 20200491 ([BLA761344 / SDN 8](#));
- Clinical Study Report for study 20160323 ([BLA761344 / SDN 8](#));
- Pharmacometrics Report 157687 includes Cardiac Assessment ([BLA761344 / SDN 8](#));
- Sponsor's Labeling ([BLA761344 / SDN 22](#));
- Highlights of clinical pharmacology and cardiac safety ([BLA 761344/ SDN 13](#)).

1 IRT Responses

Consult request: The sponsor Amgen Inc. has submitted their Pharmacometrics Report 157687 (which includes cardiac assessment), "*Exposure-Response Analysis for Efficacy and Safety of Tarlatamab in Subjects with Small Cell Lung Cancer.*" The clinical pharmacology requested a QT IRT review and wanted to highlight section 8.4 of the study report. Also, this is a large molecule/protein therapeutic (bispecific T-cell engager).

IRT's response: No clinically significant QT prolongation was observed in the sponsor's clinical and non-clinical QT assessment. Although the sponsor's pharmacometric analysis determines a statistically significant positive C-QTc relationship, this relationship is very shallow, not clinically significant, and unlikely to be due to interaction with hERG channel since tarlatamab is a large therapeutic protein made of naturally occurring amino acids. Furthermore,

categorical analysis of ECGs, and profiles of adverse events in the completed clinical studies do not suggest disproportionate increase in QT prolongation risk in patients receiving the proposed therapeutic dosing regimen. These findings are supported by nonclinical ECG data in cynomolgus monkeys exposed to ~100-fold tarlatamab concentration with no ECG abnormalities. The data presented by the sponsor do not suggest a mechanism for QT prolongation by tarlatamab.

We do not propose any QT labelling language.

2 Internal Comments for the Division

(b) (5)

3 BACKGROUND

3.1 Product Information

The sponsor, Amgen is developing Tarlatamab (AMG 757, brand name Imdeltra; molecular weight of about 105 kilodaltons) as an intravenous injection indicated for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. This indication is approved under accelerated approval based on the overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Tarlatamab is a bispecific T-cell engager (BiTE®) molecule that targets the tumor-associated antigen delta-like ligand 3 (DLL3). Tarlatamab consists of 2 single-chain variable fragment binding domains, specific for DLL3 and the T-cell receptor (TCR)-associated protein cluster of differentiation 3 (CD3), fused to a silenced fragment crystallizable (Fc) immunoglobulin domain to extend serum half-life. Tarlatamab is designed to simultaneously bind to DLL3 that is expressed on the surface of cancer cells and CD3 expressed on the surface of T cells.

The mechanism of action of tarlatamab is T cell-dependent lysis of tumor cells. The pharmacological effect of tarlatamab is mediated by specific redirection of T cells to kill DLL3-expressing tumor cells. The bispecific binding of tarlatamab to T-cells and DLL3-positive tumor cells triggers T-cell activation, production of inflammatory cytokines, release of cytotoxic proteins, which results in redirected lysis of tumor cells. The pharmacodynamic response was characterized by transient cytokine elevation and immune related biomarkers.

Tarlatamab has been developed as an injection with (1) 1 mg of lyophilized powder in a single-dose vial for reconstitution and (2) 10 mg of lyophilized powder in a single-dose vial for reconstitution. It 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. It is for injection and is supplied as a sterile, single dose, preservative free, white to slightly yellow, lyophilized powder for reconstitution.

Each 1 mg vial contains tarlatamab (1 mg), sucrose (37.1 mg), (b) (4) glutamic acid (0.72 mg), polysorbate 80 (0.04 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 of tarlatamab. Each 10 mg vial contains tarlatamab (10 mg), sucrose (194.4 mg), (b) (4) glutamic acid (3.7 mg), polysorbate 80 (0.2 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 of tarlatamab.

The recommended dosage is an initial dose of 1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter. It is administered as an intravenous infusion over 1 hour.

3.2 Sponsor's position related to the question

The sponsor posits that, as a therapeutic protein, tarlatamab is not expected to inhibit hERG channel function directly. Nevertheless, the sponsor has conducted concentration-QTc analysis of time matched PK/ECG data collected from studies 20160323 and 20200491.

Study 20160323 was a phase 1, open label, multiple ascending dose study evaluating tarlatamab monotherapy and in combination with anti-PD-1 in subjects with SCLC. Only data from monotherapy part was used for C-QTc assessment. The planned doses in the ascending monotherapy phase were: 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, and 100 mg. Doses between 0.003 – 0.1 were to be administered to one subject per dose. Doses between 3 – 100 were to be administered in steps. Different step procedures were tested e.g., 1 mg on day 1 followed by step dose on day 4 or 8 and target dose on day 15 and Q2W thereafter. Triplicate 12-lead ECGs were collected at screening, pre-dose, and at end of infusion on C1D1, C1D4, C1D8, C1D15, C2D1, C2D15, C3D1, C4D1, C4D8, and C4D15. PK samples were collected at several time points including at the end of infusion.

Study 20200491 was a phase 2, open label, registration study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of tarlatamab in subjects with recurrent SCLC. The study had 3 parts. Part 1 randomized subjects in 1:1 ratio to 10 mg or 100 mg Q2W. Part 2 was dose expansion at the selected target dose of 10 mg. Triplicate 12-lead ECGs were collected in first 50 subjects in part 1 (~25 subjects per dose level) with time matched PK at pre-infusion C1D1 and end of infusion C2D1 and C2D15.

The sponsor's C-QTc analysis included 231 subjects with baseline QTcF and post-infusion time-matched PK/ECG data.

The relationship between tarlatamab concentration and the absolute change from baseline in QTcF was evaluated by a linear mixed-effect regression analysis. Baseline QTcF was evaluated as a covariate and subject was evaluated as a random effect for intercept and/or slope in the model. The plots of model predicted tarlatamab concentrations and associated mean Δ QTcF (90% CI) were used to evaluate the concentration-response relationship.

According to the sponsor a linear mixed effect model with inter-subject variability on intercept and slope best described the relationship between tarlatamab exposure and Δ QTcF. The sponsor's final model is presented in Equation 1.

$$\Delta QTcF_{i,j} \sim (\theta_0 + \eta_{0,i}) + (\theta_1 + \eta_{1,i}) \cdot C_{i,j} + \theta_2 \cdot (QTcF_{bs,i} - QTcF_{bs,all})$$

Equation 1. Sponsor's final linear mixed effect model to describe C-QTc relationship for tarlatamab

Where $\Delta QTcF_{i,j}$ represents the absolute change in QTcF from baseline for subject i at time j ; θ_0 is the population mean intercept and $\eta_{0,i}$ is the random effect on intercept for subject i ; θ_1 is the population mean slope of the assumed linear association between concentration and $\Delta QTcF_{i,j}$, and $\eta_{1,i}$ is the random effect on the slope for subject i ; $C_{i,j}$ is the concentration for subject i at time j ; θ_2 is the fixed effect associated with the individual baseline value, $QTcF_{bs,i}$, relative to overall mean baseline QTcF value, $QTcF_{bs,all}$. The model assumed that the random effects and residual error were normally distributed with mean of zero.

Based on the sponsor's findings, a shallow but statistically significant slope was observed (Slope = 0.0000283, p-value = 0.0131). However, the model predicted mean $\Delta QTcF$ at the model estimated steady state C_{max} of 3580 ng/ml following the proposed clinical dosing regimen of 10 mg Q2W was 0.25 msec (90%CI: 0.085 – 0.42).

The sponsor's proposed label does not include any QT related labelling.

Reviewer's Comment 1: *Although the sponsor's analysis determines a statistically significant positive C-QTc relationship, this relationship is unlikely to be due to interaction with hERG channel since tarlatamab is a large protein therapeutic molecule consisting of 982 amino acids and having a molecular weight of about 105 kilodaltons. Notably, the relationship is very shallow and not clinically significant. Nonclinical ECG data from toxicology studies in Cynomolgus Monkeys receiving up to 4.5 mg/Kg (Day 85 trough concentration = 315000 ng/mL) do not show ECG abnormalities after treatment with tarlatamab (See Section 3.4). According to the ICH E14 Q&A 6.3 (R3), "Large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies". The data presented by the sponsor do not suggest a mechanism for QT prolongation by tarlatamab.*

3.3 Clinical Pharmacology

See Highlights of Clinical Pharmacology and Cardiac Safety ([link](#))

Therapeutic dose and exposure: The proposed dose and dosing regimen for tarlatamab for the treatment of adult patients with advanced SCLC with disease progression on or after platinum-based chemotherapy is an initial 1 mg dose on day 1, followed by 10 mg on day 8, day 15, and Q2W thereafter, with all doses administered via a 1-hour IV infusion.

The highest doses tested in study 20160323 (a multiple ascending dose study) were 100 mg Q2W and 200 mg Q3W.

Exposures achieved at maximum tested dose: At steady state (C2D1) following 200 mg Q3W regimen, tarlatamab mean (%CV) C_{max} was 65.3 (43.8%) $\mu\text{g/mL}$ and AUC_{504hr} was 12,100 (24.1%) $\text{h} \times \mu\text{g/mL}$ (study 20160323).

Tarlatamab exhibits dose-proportional increase in serum exposures in the evaluated dose range of 0.003 mg to 100 mg Q2W and 200 mg Q3W.

Like other biologic therapeutics and due to its large molecular size (about 105 kDa), tarlatamab is expected to be degraded into small peptides and amino acids via catabolic pathways. Tarlatamab is neither expected to be metabolized by hepatic drug metabolizing enzymes nor undergo renal glomerular filtration and excretion.

Population PK analyses showed that tarlatamab PK was not affected by age (range 32 to 82 years), sex or race. Also based on population PK analyses, the mild or moderate hepatic impairment and mild or moderate renal impairment were not correlated with tarlatamab clearance.

No formal DDI studies have been conducted for tarlatamab.

Expected High Clinical Exposure Scenario: According to the sponsor, tarlatamab is a biologic which is catabolized into small peptides or amino acids, and therefore, the pharmacokinetic DDI potential as a victim or the effect of food is expected to be negligible. Furthermore, tarlatamab clearance was not impacted by renal or hepatic organ impairment. Therefore, the expected high clinical exposure scenario would be like that of the proposed clinical regimen of 10 mg Q2W which has the observed steady state (C2D15) geometric mean (%CV) for C_{max} of 2.65 (41%) µg/mL and for AUC_{336hr} of 298 (48%) µg*hr/mL. Cardiac assessment in Report 157687 indicate that the clinical dose regimen provides a median steady state C_{max} of 3.58 µg/mL.

Table 1: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	10 mg Q2W IV Infusion	*2.65 µg/ml
Sponsor's High clinical exposure scenario	10 mg Q2W IV Infusion	2.65 µg/ml
Highest dose in QT assessment	**100 mg Q2W	***27.4 µg/ml
C_{max} Ratio	27.4/2.65 = 10.3	

*Observed geometric mean C_{max} is lower than model estimated median C_{max} of 3.58 µg/ml.

although maximum dose tested in study 20160323 is 200 mg Q3W (Part G), the highest dose in QT assessment (Part A1, A2, and A3) was 100 mg Q2W (Source CSR study 20160323 and Report #157687). *Source: Summary of clinical pharmacology studies, Table 3.

3.4 Nonclinical Cardiac Safety

Electrographic assessments were included in the 28 day and 3-month toxicological studies in cynomolgus monkeys.

In the 28-day GLP study, monkeys received slow bolus infusion of either 0, 50, 500, or 4500 µg/Kg QW for 28 days. No clinically significant ECG abnormalities were observed up mean trough concentration of 95100 ng/ml in 6 monkeys receiving 4500 µg/Kg. However, on day 2 of

this study, there were slight tarlatamab-related increases in heart rate at ≥ 500 $\mu\text{g/kg}$ that were associated with decreased PR, RR, and QT intervals. Throughout the 24-hour collection period, the mean change in heart rate was less than 10% higher than the control group (individual changes up to 23% were recorded). These changes were not evident in any animal regardless of anti-drug antibody (ADA) status on day 23, the next point at which they were measured. Given the low magnitude of the heart rate increase and the absence of an effect at the end of study despite continued dosing, this finding was not considered adverse. There were no tarlatamab-related neurological observations or changes in body temperature or respiratory rate in the 28-day toxicology study.

In the 3-month toxicology study, monkeys received slow bolus injection of either 0, 50, or 4500 $\mu\text{g/Kg}$. Up to mean trough concentration of 315000 ng/ml of day 85 in monkeys receiving 4500 $\mu\text{g/Kg}$ there were no tarlatamab-related changes in the following parameters: electrocardiograms, body temperature, respiration rates, and neurological examinations. Furthermore, no treatment-related macroscopic or microscopic changes were detected in the heart.

3.5 Clinical Cardiac Safety

The clinical cardiac safety of tarlatamab is summarized in the [table of highlights of clinical pharmacology and cardiac safety](#). Briefly, the sponsor presents findings from concentration-QTc, categorical analysis and description of peculiar ECGs from studies 20200491 and 20160323. The sponsor summarizes the findings as follows:

- There were no subjects with a QTcF maximum value post-baseline > 500 msec at the planned dose of 10 mg in subjects with SCLC (n=160). There were no subjects with a QTcF maximum value postbaseline > 500 msec at the 100 mg dose (n=163).
- One subject (0.6%) in the 10 mg dose group (n=160) had a change from baseline QTcF of >60 msec after receiving tarlatamab, with 1 reported adverse event of AMG 757 medication overdose, which was inadvertently prepared by the pharmacy at 23.8 mg instead of 10 mg of tarlatamab. No adverse events due to the overdose were reported. No AEs potentially related to the increase in QTcF were reported.
- There were 2 subjects (1.2%) in the 100 mg dose group (n=163) with maximum post baseline QTcF interval of > 480 to 500 msec. Both subjects were enrolled in study 20200491. Both subjects had SCLC stage IV, and were treated with tarlatamab at a dose of 100 mg. One subject had a change from baseline QTcF of approximately 30 msec (on cycle 2 day 15) and one subject had a change from baseline of QTcF of approximately 7 msec (on cycle 1 day 1) after receiving tarlatamab dose of 100 mg with no reported adverse events potentially related to the increase in QTcF interval.
- One subject (0.6%) in the 100 mg dose group had a change from baseline QTcF of >60 msec, after receiving tarlatamab dose of 100 mg with no reported adverse events potentially related to the increase in QTcF.
- The subject incidence of the AEs as MedDRA preferred terms as noted by the Agency in the instructions at the proposed dose of 10 mg in subjects with SCLC (n=160) was as follows: electrocardiogram QT prolonged (0.6%), syncope (1.9%), seizures (0.0%), ventricular arrhythmias (0.0%), ventricular tachycardia (0.0%), ventricular fibrillation

(0.0%), atrial flutter (0.0%), cardiac flutter (0.0%), torsade de pointes (0.0%), and sudden death (0.0%).

- The subject incidence of the AEs as MedDRA preferred terms as noted by the Agency in the instructions at the dose of 100 mg in subjects with SCLC (n=163) was as follows: electrocardiogram QT prolonged (2.5%), syncope (1.2%), seizures (1.2%), ventricular arrhythmias (0.0%), ventricular tachycardia (0.6%), ventricular fibrillation (0.0%), atrial flutter (0.6%), cardiac flutter (0.0%), torsade de pointes (0.0%), and sudden death (0.0%).
- The subject incidence of the AEs as MedDRA preferred terms as noted by the Agency in the instructions at any dose and any indication in the monotherapy studies (N=457) was as follows: electrocardiogram QT prolonged (2.4%), syncope (1.1%), seizures (0.9%), ventricular arrhythmias (0.0%), ventricular tachycardia (0.2%), ventricular fibrillation (0.0%), atrial flutter (0.4%), cardiac flutter (0.2%) torsade de pointes (0.0%), and sudden death (0.0%).
- Medical review by Amgen of these and all other cardiac events from the clinical trial integrated analysis of safety (ISS) dataset did not suggest a risk of potential cardiac toxicity with tarlatamab treatment at the intended dose in the monotherapy studies.

Overall, no clinically significant electrocardiogram (ECG) findings have been observed in ongoing tarlatamab studies, this is consistent with tarlatamab being a protein therapeutic (molecular weight of ~105 KDa) which is not expected to inhibit human ether-a-go-go related gene channel function directly.

3.6 Summary results of prior QTc assessments

No prior QTc assessments were reviewed by IRT previously.

3.7 Relevant details of planned Phase 2/3 study

The sponsor is currently conducting study 20210004. This is a phase 3, randomized open-label study evaluating the efficacy and safety of tarlatamab compared with standard of care (SOC) therapy in subjects with small-cell lung cancer (SCLC) who have progressed after 1 prior line of platinum-containing therapy.

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Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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RAMAN K BAWEJA
02/08/2024 10:53:04 AM

ELIFORD N KITABI
02/08/2024 10:58:57 AM

CHRISTINE E GARNETT
02/08/2024 12:01:07 PM