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APPLICATION NUMBER:

761312Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

CLINICAL PHARMACOLOGY MEMO

NDA Number	BLA 761312 (SDN 42)
Link to EDR	\\CDSESUB1\evsprod\BLA761312\0042
Submission Date	03/14/2024
Submission Type	Class 2 Resubmission
Product Name	Lymphir (denileukin diftitox-cxdl) for injection, for intravenous use
Generic Name	Ontak
Dosage Form and Strength	300 mcg lyophilized cake in a single-dose vial
Route of Administration	Intravenous (IV) infusion
Proposed Indication(s)	For treatment of adult patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy
Proposed dosing regimen	9 mcg/kg/day actual body weight administered as an intravenous infusion on Days 1 through 5 of a 21-day cycle.
Applicant	Citius Pharmaceuticals Inc.
OCP Review Team	Frank Green, Pharm.D., M.S.; Nan Zheng, Ph.D.
OCP Final Signatory	Brian Booth, Ph.D.

1. Executive summary

Citius Pharmaceuticals Inc. (the Applicant) submitted a Class 2 Resubmission of a Biologics License Application (BLA) for Lymphir (denileukin diftitox-cxdl) for injection.

BLA 761312 was originally submitted on September 28, 2022. It was issued a Complete Response (CR) Letter on July 28, 2023, due to product quality issues (Reference ID: 5216972). The Office of Clinical Pharmacology reviewed the information included in the original BLA for Lymphir and concluded that it was approvable from a clinical pharmacology perspective (Reference ID: 5216748, Section 6).

The resubmission for Lymphir contains updated immunogenicity datasets as the only new information related to clinical pharmacology. This review evaluates the adequacy of the updated immunogenicity assessment and reporting in Section 12 of the product label. Data included in the original BLA submission was previously evaluated and has not been reassessed in this review.

1.1. Conclusions:

The Office of Clinical Pharmacology has reviewed the updated immunogenicity datasets included in this resubmission for Lymphir for accuracy of reporting in the proposed labeling. The presence of anti-drug antibodies (ADA) for denileukin diftitox-cxdl and IL-2 is associated with a reduction in the measured denileukin diftitox-cxdl concentration but does not appear to adversely impact safety and efficacy.

2. Comprehensive clinical pharmacology review

During the original BLA submission review, the Applicant submitted an amendment with updated immunogenicity datasets on July 26, 2023 (Submission 0040), that could not be reviewed ahead of the issuance of the CR letter. This amendment was in response to two clinical pharmacology information requests on June 28, 2023 and July 6, 2023 requesting that the Applicant update the immunogenicity datasets based on an updated screening cut-point and normalization factor. Updating the immunogenicity datasets with these numbers reported the following values:

1. The number of patients from clinical study E7777-G000-302 (Study 302) evaluable for immunogenicity at baseline decreased from 91 to 90, due to one patient flagged by the bioanalytical laboratory as not reportable. The number of patients evaluable for treatment-emergent immunogenicity was not affected.
2. Of the patients with immunogenicity results at baseline, the reported immunogenicity values are as follows:
 - a. The pre-existing antibodies to denileukin diftitox-cxdl were 74% (67/90) and neutralizing anti-denileukin diftitox-cxdl were 7.8% (7/90).
 - b. The pre-existing antibodies to IL-2 were 5.6% (5/90) and zero patients with neutralizing antibodies.
3. Of the patients who developed treatment-emergent ADAs (i.e., treatment-induced or treatment-boosted) following denileukin diftitox-cxdl administration, the reported immunogenicity values are as follows:
 - a. Eighty-eight percent (74/84) of patients developed ADAs against denileukin diftitox-cxdl. Additionally, 80% (67/84) of patients developed neutralizing antibodies against denileukin diftitox-cxdl.
 - b. Eight-two percent (69/84) of patients developed ADAs against IL-2, and the number of patients who developed neutralizing antibodies against the IL-2 domain of denileukin diftitox-cxdl was 13% (11/84).
4. The updated datasets showed that the median anti-denileukin diftitox-cxdl antibody titers were 182, 260, 153, and 94 times higher than baseline at C2D1, C3D1, C5D1, and C8D1 and the anti-IL2 antibody titers were 2, 49, 437, and 1312 times higher than baseline, in subjects with treatment-emergent ADA.
5. In patients with intensive PK collection and treatment-emergent ADA, the percent geometric mean ratio for denileukin diftitox-cxdl C_{max} and $AUC_{(0-t)}$ is 37% and 19% in Cycle 3 compared to Cycle 1, and is 30% and 15% in Cycle 5 compared in Cycle 1.

The incidence rates of major adverse events (i.e., capillary leak syndrome, blurred vision, infusion related reactions, hepatotoxicity) in patients who received the 9 mcg/kg/day dose in Study 302 and developed treatment-emergent ADAs (N=76) are comparable to those in the overall safety population (N=119). The objective response rate (ORR) in the overall efficacy population (N=69; ORR=36%) were driven by the ADA positive patients (N=57; ORR=40%). The small number of patients without treatment-emergent ADA prevented direct comparison of efficacy and safety responses between the ADA positive and negative groups.

Overall, the immunogenicity data suggests that the high rates of both baseline and treatment-emergent ADA for denileukin diftitox-cxdl and/or IL-2 that reduce the measured serum concentrations of denileukin diftitox-cxdl are not of major concern. Updating the

immunogenicity datasets with the new screening cut-point and normalization factor result in changes to the reported immunogenicity values but do not affect previous conclusions that neither the high rates of ADA nor the differences in serum concentration have clinically significant impacts on safety and efficacy.

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CLINICAL & LABELING REVIEW

Application Number(s)	BLA 761312
Established/Proper Name	LYMPHIR
Applicant	Citius Pharmaceuticals, Inc.
Submit Date	2/13/2024
Received Date	2/13/2024
PDUFA Goal Date	8/13/2024
Division/Office	Division of Hematologic Malignancies II / OOD
Clinical Reviewers	Shyamli Singla, MD (primary) Nicholas Richardson, DO, MPH (clinical team lead)
Associate Director of Labeling	Elizabeth Everhart, MSN, RN, ACNP
Deputy Division Director	Nicholas Richardson, DO, MPH
Division Director (OOD)	Nicole Gormley, MD
Approved Indication	An IL2-receptor-directed cytotoxin indicated for the treatment of adult patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.
Completion Date	7/30/2024
Recommendation	Traditional Approval

Table of Contents

1. Executive Summary	3
2. Regulatory Background	3
3. Labeling Recommendations	3
4. Postmarketing Requirements and Commitments.....	5

1. Executive Summary

BLA 761312, initially received on 9/28/2022, was submitted for the review of denileukin diftitox (LYMPHIR), an intravenously administered, IL-2-receptor-directed cytotoxin. The application was primarily based on data from Study E7777-G000-302: "A Clinical Study to Demonstrate Safety and Efficacy of E7777 in Persistent or Recurrent Cutaneous T-Cell Lymphoma," with supplementary data from Study E7777-J081-101 and E7777-J081-205. On 7/27/2023, the FDA review team recommended a complete response of LYMPHIR for the treatment of patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy. The recommendation of a complete response was based on multiple product quality deficiencies that were identified and not adequately addressed during the BLA assessment period, including issues related to endotoxin level testing, the manufacturing process, sterilization validation, amongst several other quality issues. For the initial BLA clinical review, refer to the NDA/BLA Multi-disciplinary Review and Evaluation filed in DARRTS on 7/28/2023.

The re-submission of BLA 761312 provides no additional updates to inform efficacy or safety, but does provide acceptable resolutions to the prior quality deficiencies that were identified in the initial review. Refer to CMC's separate review memo for additional details. The USPI was updated accordingly to reflect these changes. Additionally, as determined during the initial BLA review, the review team issued one postmarketing requirement (PMR) which aims to address the need for additional data to characterize ophthalmologic toxicity in patients receiving E7777.

2. Regulatory Background

Denileukin diftitox initially received accelerated approval (BLA 103767) in 1999 for the treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor. The product's proprietary name was ONTAK, and it received traditional approval in 2008 following results of the double-blind, randomized, placebo-controlled Phase 3 study (Study 93-04-11).

The accelerated approval of ONTAK included a PMR to improve the purification process to increase product purity, and this requirement was fulfilled in 2009. However, the product was determined by the FDA to be a new product, and in 2011 a new IND for the revised product (referred to as E7777) was submitted to replace ONTAK (b) (4). Given the prior regulatory approval of ONTAK (same active ingredient as E7777) based on randomized data in patients with CTCL, the FDA agreed that a single-arm trial of E777 may be used to support an

application seeking traditional approval. In 2014, ONTAK production was discontinued due to manufacturing issues.

The original BLA for denileukin diftitox (LYMPHIR) was submitted on 9/28/2022. Substantial evidence of efficacy of denileukin diftitox in patients with relapsed or refractory Stage I-III CTCL was based on overall response rate (ORR) in Study 302, a single-arm, multicenter trial of denileukin diftitox in patients with CTCL. Sixty-nine patients with Stage I-III CTCL who previously received 1 prior systemic therapy and received denileukin diftitox at the recommended dosage were evaluable for efficacy. In the efficacy population, all patients had at least 1 prior systemic therapy and the median number of prior therapies was 4 (range: 1-18). By independent review committee (IRC) assessment, the ORR was 36.2% (95% CI: 25.0, 48.7) and the complete remission (CR) and partial response (PR) rates were 9% and 27% respectively, according to the Olsen (2011) criteria, with a median time to response of 1.4 months. Out of the 25 respondents, none experienced an event (progression or death). The median duration of response using Kaplan-Meier (KM) estimate could not be determined as all responders were censored. In patients who achieved a response, the duration of response exceeded 6 months in 52% (13/25) and 12 months in 20% (5/25). While the data related to durability of response were limited by the degree of censoring, the ORR supported the determination that denileukin diftitox has clinically meaningful activity in patients with relapsed or refractory Stage I-III CTCL.

The safety of denileukin diftitox was evaluated in 119 patients with relapsed or refractory Stage I-IV CTCL across three clinical trials. Patients received treatment with denileukin diftitox 9 mcg/kg daily from Day 1 through Day 5 of each 21-day cycle. Treatment was administered until disease progression or unacceptable toxicity. The median number of cycles was 5 (range: 1 to 42), with 13% exposed for 6 months or longer. Serious adverse events (SAEs) occurred in 38% of patients, most often from capillary leak syndrome, infusion-related reaction, or sepsis. Adverse events (AEs) leading to treatment discontinuation occurred in 15% of patients, treatment interruption in 33%, and dose reductions in 4%. The most common reasons for treatment modification were capillary leak syndrome and infusion-related reaction. A fatal AE of capillary leak syndrome occurred in 1 patient. The most common ($\geq 20\%$) adverse events, including laboratory abnormalities, were increased transaminases (70%), albumin decreased (53%), nausea (40%), edema (35%), hemoglobin decreased (34%), fatigue (30%), musculoskeletal pain (26%), rash (23%), chills (22%), constipation (22%), pyrexia (21%), and capillary leak syndrome (20%).

Based on ORR and durability, denileukin diftitox has demonstrated meaningful clinical activity in this patient population, along with an acceptable safety profile to support the following indication: The treatment of patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

For additional information, refer to the NDA/BLA Multi-disciplinary Review and Evaluation filed in DARRTS on 7/28/2023.

3. Labeling Recommendations

For the review of the U.S. Prescribing Information (USPI) in the last cycle – see the multidisciplinary review filed in DARRTS on July 28, 2023.

During this review cycle, the following edits were made by the FDA to the USPI:

- Throughout the USPI, the identifying characteristics of the product were changed from (b) (4) " to "lyophilized cake" based on submitted data.
- In subsection 2.1 Important Dosing Instructions, the subsection title was corrected.
- In subsection 2.3 Recommended Premedications, a missing unit of measurement was added to Table 1.
- In subsection 2.4 Dosage Modifications for Adverse Reactions, a dose reduction of 50% was added to Table 2 in the recommendations for dosage modifications for Grade 3 hepatotoxicity as it is consistent with what was done during the clinical trial for hepatotoxicity.
- In subsection 2.5 Preparation and Administration, the temperature range for reaching room temperature was added and the required statement about visually inspecting parenteral products was added.
- In subsection 5.1 Capillary Leak Syndrome, the first sentence was changed from " (b) (4) " to "Lymphir can cause...,including life-threatening or fatal reactions." to align with the text in the Boxed Warning.
- In subsection 5.2 Visual Impairment, the text in the last paragraph was modified to align with the text in the Highlights that recommends that Lymphir be withheld until visual impairment resolves.
- In subsection 5.3 Infusion-Related Reactions, the last paragraph was modified to align with the text in the Highlights that recommends interrupting ((b) (4)) Lymphir based on severity.
- In subsection 5.4 Hepatotoxicity, the laboratory data show ALT/AST elevations indicative of hepatotoxicity and so the first sentence of the warning was revised to say that "Lymphir can cause hepatotoxicity" from (b) (4) ". The recommendations in the last paragraph were modified to align with recommendations in Table 2 in subsection 2.4 to reduce the dose in addition to withholding or permanently discontinuing Lymphir.
- In subsection 6.1 Clinical Trials Experience, a missing cross-reference to the clinical studies section was added.
- In subsection 12.3 Pharmacokinetics within the heading Specific Populations, body weight (39 kg to 148 kg) was added to the paragraph that states no clinically significant differences in pharmacokinetics. Initially the label included (b) (4)

- (b) (4)
- In subsection 12.6 Immunogenicity, a paragraph proposed by the applicant (b) (4) was removed as it does not offer useful information for healthcare practitioners. References to (b) (4) were changed to “Study 302” to align with the rest of the USPI where the actual study number was used. Baseline numerator was updated to include patients with negative ADA at baseline since they are also included in the denominator. Within the ADA effects on pharmacokinetics heading, the data was updated to include the geometric mean ratio.

4. Postmarketing Requirements and Commitments

The review team recommends one safety postmarketing requirement (PMR), which aims to address the need for additional data to characterize ophthalmologic toxicity in patients receiving E7777 and inform patient labeling regarding risk, recommended assessments and mitigation strategies. For additional information on the assessment of visual impairment, refer to the NDA/BLA Multi-disciplinary Review and Evaluation filed in DARRTS on 7/28/2023.

Postmarketing requirement:

Conduct a clinical study to further characterize the known serious risk of visual impairment including risk factors, manifestations, and outcomes in patients with cutaneous T-cell lymphoma (CTCL) treated with denileukin diftitox-cxdI. The visual impairment monitoring procedures in this study should include, but should not be limited to, visual acuity, slit lamp examination, dilated funduscopic examination, and optical coherence tomography. The study will ascertain for and closely monitor any potential risk factors associated with visual impairment. Evaluate patients with CTCL treated with denileukin diftitox-cxdI and provide data on at least 50 patients with visual impairment that occurred on denileukin diftitox-cxdI treatment.

Draft Protocol Submission:	12/2024
Final Protocol Submission:	05/2025
Trial Completion:	05/2028
Final Report Submission:	09/2028

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MEMORANDUM

Date: July 29, 2024
To: File for BLA 761312
From: Moran Choe, PhD
Pharmacology/Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Office of Oncologic Diseases (OOD)
Through: Brenda J Gehrke, PhD
Pharmacology/Toxicology Supervisor
Subject: Nonclinical review for BLA 761312
File: BLA 761312
Applicant: Citius Pharmaceuticals, Inc.
Drug: Lymphir (denileukin diftitox-cxdl)
Indication: The treatment of adult patients with relapsed or refractory stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy

Lymphir (denileukin diftitox-cxdl), an IL-2-receptor-directed cytotoxin, is a recombinant DNA-derived fusion protein composed of the amino acid sequences for diphtheria toxin (DT) fragments A and B (Met1-Thr387)-His and the sequence for human interleukin-2 (IL-2; Ala1-Thr133). It is designed to direct the cytotoxic action of DT to cells that express the IL-2 receptor. After uptake into the cell, the DT fragment is cleaved and the free DT fragments inhibit protein synthesis, resulting in cell death. BLA 761312 was submitted on September 28, 2022, and the FDA issued a complete response (CR) letter for this application on July 28, 2023, due to product quality deficiencies. The Applicant submitted a complete response to the CR letter as a Class 2 resubmission for BLA 761312 on February 13, 2024. There were no new nonclinical data submitted for this BLA resubmission. There are no approvability issues from the Pharmacology/Toxicology perspective.

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NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original BLA
Application Number(s)	BLA 761312
Priority or Standard	Standard
Submit Date(s)	September 28, 2022
Received Date(s)	September 28, 2022
PDUFA Goal Date	July 28, 2023
Division/Office	Division of Hematologic Malignancies II/Office of Oncologic Diseases
Review Completion Date	July 27, 2023
Established Name	Denileukin diftitox
(Proposed) Trade Name	Lymphir
Pharmacologic Class	Denileukin diftitox is a recombinant cytotoxic fusion protein consisting of diphtheria toxin fragments A and B and human interleukin-2; IL2-receptor-directed cytotoxin
Code name	E7777
Applicant	Citius Pharmaceuticals, Inc.
Formulation(s)	300 mcg lyophilized powder in a single dose
Dosing Regimen	9 µg/kg/day administered as an intravenous (IV) infusion over 60 minutes on Days 1 through 5 of 21-day cycle; administered until disease progression or unacceptable toxicity.
Applicant Proposed Indication(s)/Population(s)	(b) (4) indicated for the treatment of adult patients with persistent or recurrent cutaneous T-cell lymphomas after at least 1 prior systemic therapy, (b) (4) (b) (4)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	An IL2-receptor-directed cytotoxin indicated for the treatment of adult patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation.....	9
Additional Reviewers of Application	9
Glossary	11
1 Executive Summary.....	13
1.1 Product Introduction	13
1.2 Conclusions on the Substantial Evidence of Effectiveness.....	13
1.3 Benefit-Risk Assessment (BRA)	15
1.4 Patient Experience Data	18
2 Therapeutic Context	20
2.1 Analysis of Condition	20
2.2 Analysis of Current Treatment Options	21
3 Regulatory Background.....	26
3.1 U.S. Regulatory Actions and Marketing History	26
3.2 Summary of Presubmission/Submission Regulatory Activity.....	26
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	28
4.1 Office of Scientific Investigations (OSI)	28
4.2 Product Quality.....	28
4.3 Clinical Microbiology	28
4.4 Devices and Companion Diagnostic Issues	29
5 Nonclinical Pharmacology/Toxicology	30
5.1 Executive Summary	30
5.2 Referenced NDAs, BLAs, DMFs	32
5.3 Pharmacology	32
5.4 ADME/PK	36
5.5 Toxicology.....	37
5.5.1. General Toxicology	37
5.5.2. Genetic Toxicology	49
5.5.3. Carcinogenicity	50
5.5.4. Reproductive and Developmental Toxicology	50
5.5.5. Other Toxicology Studies.....	51

6	Clinical Pharmacology.....	52
6.1	Executive Summary	52
6.2	Summary of Clinical Pharmacology Assessment.....	54
6.2.1.	Pharmacology and Clinical Pharmacokinetics.....	54
6.2.2.	General Dosing and Therapeutic Individualization	56
6.2.2.1.	General Dosing	56
6.2.2.2.	Therapeutic Individualization	56
6.2.2.3.	Outstanding Issues	58
6.3	Comprehensive Clinical Pharmacology Review.....	58
6.3.1.	General Pharmacology and Pharmacokinetic Characteristics.....	58
6.3.2.	Clinical Pharmacology Questions.....	60
7	Sources of Clinical Data.....	69
7.1	Table of Clinical Studies.....	69
8	Statistical and Clinical Evaluation.....	72
8.1	Review of Relevant Individual Trials Used to Support Efficacy	72
8.1.1.	Study E7777-G000-302.....	72
8.1.2.	Study Results for E7777-G000-302	78
8.1.3.	Supportive Study E7777-J081-205.....	91
8.1.4.	Study Results for Supportive Study E7777-J081-205	94
8.1.5.	Supportive Study E7777-J081-101.....	100
8.1.6.	Study Results for Supportive Study E7777-J081-101	103
8.1.7.	Integrated Review of Effectiveness	107
8.1.8.	Assessment of Efficacy Across Trials.....	108
8.1.9.	Integrated Assessment of Effectiveness	111
8.2	Review of Safety	112
8.2.1.	Safety Review Approach.....	112
8.2.2.	Review of the Safety Database	114
8.2.3.	Adequacy of Applicant’s Clinical Safety Assessments.....	117
8.2.4.	Safety Results	119
8.2.5.	Analysis of Submission-Specific Safety Issues.....	142
8.2.6.	Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability	142

8.2.7. Safety Analyses by Demographic Subgroups	142
8.2.8. Specific Safety Studies/Clinical Trials.....	143
8.2.9. Additional Safety Explorations.....	143
8.2.10. Safety in the Postmarket Setting.....	144
8.2.11. Integrated Assessment of Safety.....	145
SUMMARY AND CONCLUSIONS	146
8.3 Statistical Issues.....	146
8.4 Conclusions and Recommendations.....	147
9 Advisory Committee Meeting and Other External Consultations	149
10 Pediatrics	149
11 Labeling Recommendations.....	150
12 Risk Evaluation and Mitigation Strategies (REMS)	153
13 Postmarketing Requirements and Commitment	154
14 Division Director (DHOT) (NME ONLY)	154
15 Division Director (OCP)	154
16 Division Director (OB)	155
17 Division Director (Clinical).....	155
18 Office Director (or designated signatory authority).....	155
19 Appendices	157
19.1 References.....	157
19.2 Financial Disclosure	159
19.3 Nonclinical Pharmacology/Toxicology	162
19.4 OCP Appendices (Technical documents supporting OCP recommendations).....	162
19.4.1. Summary of Bioanalytical Method Validation and Performance.....	162
19.4.2. Pharmacometrics Review	165
19.4.2.1. Results of Sponsor’s Analysis.....	165
19.4.2.1.1. Population PK analysis.....	165
19.4.2.1.2. Exposure-response analysis for efficacy	173

19.4.2.1.3. Exposure-response analysis for safety.....	174
19.4.2.2. Reviewer’s Analysis.....	180
19.4.2.2.1. Background.....	180
19.4.2.2.2. Objectives.....	181
19.4.2.2.3. Results.....	181
19.5 FDA Grouped Preferred Terms	190

Table of Tables

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication	23
Table 2: Summary of Key Regulatory Events submitted to E7777 IND 1104899	27
Table 3: Key Clinical Pharmacology Review Issues	53
Table 4: Listing of Clinical Trials Relevant to this BLA.....	69
Table 5: Study E7777-G000-302 Protocol Amendments	75
Table 6: Subject Disposition and Reasons for Treatment Discontinuation in Study E7777-G000-302	79
Table 7: Demographic and Baseline Characteristics of Subjects: Study E7777-G000-302	80
Table 8: Disease Characteristics of Subjects: Study E7777-G000-302	82
Table 9: Prior Anticancer Therapy: Study E7777-G000-302	82
Table 10: Summary of Objective Response Rate E7777 9 µg/kg: Study E7777-G000-302.....	84
Table 11: Study E7777-J081-205 Protocol Amendments	94
Table 12: Demographic Characteristics of Subjects: Study E7777-J081-205	96
Table 13: Study E7777-J081-101 Protocol Amendments	102
Table 14: Demographic Characteristics of Subjects: Study E7777-J081-101	104
Table 15: Summary and Description of Safety Analysis Sets	113
Table 16: Summary of Administration of E7777.....	115
Table 17: E7777: Summary of Serious Adverse Events Occurring in 2% or More of Subjects in Any Safety Analysis Set	120
Table 18: FDA Summary of Serious Adverse Events.....	121
Table 19: E7777: Summary of Adverse Events Leading to Treatment Discontinuation.....	121
Table 20: FDA Summary of Adverse Events Leading to Treatment Discontinuation	122
Table 21: E7777: Summary of Adverse Events Leading to Dose Modification.....	123
Table 22: FDA Summary of Adverse Events Leading to Dose Reduction or Interruption	124
Table 23: FDA Summary of Capillary Leak Syndrome.....	127
Table 24: FDA Summary of Hepatotoxicity.....	128
Table 25: FDA Summary of Hypersensitivity	129
Table 26: FDA Summary of Infections	130
Table 27: FDA Summary of Infusion-related Reaction.....	131
Table 28: FDA Summary of Visual Impairment.....	132
Table 29: Summary of Treatment-Emergent Adverse Events	133
Table 30: Treatment-Emergent Adverse Events Occurring in at Least 10% of Subjects by Preferred Term and in Decreasing frequency in Any Safety Set.....	134
Table 31: FDA Summary of Treatment Emergent Adverse Events in ≥ 15% of Patients	135
Table 32: Hematology Laboratory Abnormalities.....	136
Table 33: Clinical Chemistry Laboratory Abnormalities.....	138
Table 34: Bioanalytical Method Validation Summary for E7777 Quantification for Studies E7777-G000-302 and E7777-J081-205	162

Table 35: Bioanalytical Method Validation Summary for E7777 Quantification for Study E7777-J081-101.....	164
Table 36: Number of Subjects and PK Samples per Subject by Study and Treatment Group for the Population PK Analysis Dataset.....	166
Table 37: Summary of Demographic Variables for the Population PK Analysis Dataset.....	166
Table 38: Summary of Liver Function and Disease Variables for the Population PK Analysis Dataset.....	167
Table 39: Final Population PK Model Parameters	168
Table 40: Summary of Demographic Variables of the ER for Safety Dataset.....	175
Table 41: Summary of Disease and Laboratory Variables of the ER for Safety Dataset.....	176
Table 42: Summary of Adverse Events of Special Interest of the ER for Safety Dataset.....	178
Table 43: Summary of the Efficacy Results for E7777 Clinical Programs	180
Table 44: Summary of the Safety Results for E7777 Clinical Programs	181
Table 45: FDA Grouped Preferred Terms	190

Table of Figures

Figure 1: Predicted E7777 AUC vs. Best Observed Response (BOR) per Olsen Criteria Assessed by IRC.....	62
Figure 2: Correlation Between ORR and AUC From Time 0 to 21 Days	63
Figure 3: Correlation Between AUC From Time 0 to Day 21 and the Probability of CLS or Hepatotoxicity.....	64
Figure 4: Individual E7777 Plasma Concentration Over Time Stratified by ADA Status.....	66
Figure 5: Subjects Who Met Eligibility Criteria in Study E7777-G000-302.....	75
Figure 6: Waterfall Plot for Skin Tumor Burden (mSWAT Score) – Independent Review Committee Assessment – Primary Efficacy Analysis Set	87
Figure 7: Kaplan-Meier Plot of Duration of Response - Independent Review Committee (IRC) Assessment per Olsen 2011 - Treating Disease Progression/Start of New Anticancer Therapy as Events – Primary Efficacy Analysis Set.....	88
Figure 8: Scatterplot for CD25 Expression by Subjects with or without Objective Response ^a	90
Figure 9: Tumor Response by CD25 Expression ^a	91
Figure 10: DV vs. PRED (top)/iPRED (bottom) for the Final Population Model Stratified by Study	169
Figure 11: CWRES vs. Time for the Final Population Model Stratified by Study	170
Figure 12: IWRES vs. Time for the Final Population Model Stratified by Study	171
Figure 13: Visual Predictive Check for the Final Population PK Model Stratified by Study.....	172
Figure 14: Typical Patient E7777 Plasma Concentration Over Time Profile Over 6 Cycles of Treatment with 9 mcg/kg/day E7777.....	173
Figure 15: Predicted E7777 AUC _{0-inf} vs. Best Observed Response (BOR) per Olsen Criteria Assessed by IRC.....	174
Figure 16: Population PK Prediction vs. Observation for E7777-J081-101	182

Figure 17: Population PK Prediction vs. Observation for E7777-J081-205 182
Figure 18: Population PK Prediction vs. Observation for E7777-G000-302 183
Figure 19: Correlation Between ORR and AUC From Time 0 to 21 Days 185
Figure 20: Correlation Between ORR and AUC From Time 0 to 21 Days (primary efficacy analysis set) 185
Figure 21: Correlation Between CLS and AUC From Time 0 to 21 Days..... 186
Figure 22: Correlation Between Hepatotoxicity and AUC from Time 0 to 21 Days 187
Figure 23: ADA Emerging Time..... 188
Figure 24: Individual E7777 Plasma Concentration Over Time Stratified by ADA..... 189

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NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

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OBP= Office of Biotechnology Products
 OPMA=Office of Pharmaceutical Manufacturing Assessment
 OPRO=Office of Program and Regulatory Operations
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OCP=Office of Clinical Pharmacology
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DPM=Division of Pharmacometrics
 DRM=Division of Risk Management
 DVP= Division of Pharmacovigilance

Glossary

Ab	antibody
AE	adverse event
AESI	adverse events of special interest
BLA	biologics license application
BOR	best overall response
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CLS	capillary leak syndrome
CMC	chemistry, manufacturing, and controls
CR	complete response
CRF	case report form
CRR	complete response rate
CSR	clinical study report
CTCL	cutaneous T-cell lymphoma
DD	denileukin diftitox
DLT	dose-limiting toxicity
DOR	duration of response
DT	diphtheria toxin
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
ESEC	Efficacy and Safety Evaluation Committee
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
GRS	Global Response Score
HDAC	histone deacetylase
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
LDH	lactate dehydrogenase
IL-2	interleukin 2
IND	Investigational New Drug
IRC	Independent Review Committee
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities

MF	mycosis fungoides
mSWAT	modified Severity Weighted Assessment Tool
MTD	maximum tolerated dose
Nab	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PR	partial response
PRO	patient reported outcome
PT	preferred term
PTCL	peripheral T-cell lymphoma
Q	quartile
QoL	quality of life
SAE	serious adverse event
SD	stable disease
sIL-2R	soluble IL-2 receptor
SS	Sézary syndrome
TEAE	treatment-emergent adverse event
Treg	regulatory T-lymphocytes
TTP	time to progression
TTR	time to response

1 Executive Summary

1.1 Product Introduction

Denileukin diftitox is an intravenously administered, IL-2-receptor-directed cytotoxin. The FDA review team recommends a complete response of denileukin diftitox for the treatment of patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy. The recommended dosage is 9 µg/kg/day IV over 60 minutes on Days 1 through 5 of a 21-day treatment cycle administered until disease progression or unacceptable toxicity.

The recommendation of a complete response is based on multiple product quality deficiencies that were identified and not adequately addressed during the BLA assessment period. The main product quality issues include:

1. There is no appropriate assay for endotoxin level measurement and a lack of controls for endotoxin testing on ^{(b) (4)} drug substance (DS) and drug product (DP) release ^{(b) (4)}.
2. Inadequate information demonstrating sufficient knowledge of and direct control over the manufacturing process.
3. Insufficient sterilization validation data for contact materials used in DP manufacturing.
4. Insufficient data to support adequacy of the DS bioburden control strategy and bioburden method.
5. Insufficient data to support the Reference Standard qualification and requalification protocols.
6. Insufficient data for validation of the DP batch range.

1.2 Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of efficacy of denileukin diftitox in patients with relapsed or refractory Stage I-III CTCL is based on overall response rate (ORR) in Study 302, a single-arm, multicenter trial of denileukin diftitox in patients with CTCL. Sixty-nine patients with Stage I-III CTCL who previously received 1 prior systemic therapy and received denileukin diftitox at the recommended dosage were evaluable for efficacy. In the efficacy population, all patients had at least 1 prior systemic therapy and the median number of prior therapies was 4 (range: 1-18). By independent review committee (IRC) assessment, the ORR was 36.2% (95% CI: 25.0, 48.7) and the complete remission (CR) and partial response (PR) rates were 9% and 27% respectively, according to the Olsen (2011) criteria, with a median time to response of 1.4 months. Out of the

25 respondents, none experienced an event (progression or death). The median duration of response using Kaplan-Meier (KM) estimate could not be determined as all responders were censored. In patients who achieved a response, the duration of response exceeded 6 months in 52% (13/25) and 12 months in 20% (5/25).

While the data related to durability of response are limited by the degree of censoring, the ORR supports the determination that denileukin diftitox has clinically meaningful activity in patients with relapsed or refractory Stage I-III CTCL.

(b) (4)

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Efficacy: The efficacy of denileukin diftitox is based on IRC-assessed ORR in Study 302, a single-arm trial that enrolled patients with relapsed or refractory Stage I-III CTCL, after at least 1 prior line of systemic therapy. In the efficacy population (n=69), the median number of prior systemic therapies was 4 (range: 1-18). All patients received at least 1 prior systemic therapy. The ORR per IRC was 36.2% (95% CI: 25.0, 48.7) and the CR and PR rate was 9% and 27% respectively, according to the Olsen (2011) criteria. The median time to response was 1.4 months (range: 0.7 to 5.6 months). The median (95% CI) DOR using Kaplan-Meier (KM) estimate was not estimable (NE) among the 25 responders due to censoring. In the 25 patients who achieved a response, the duration of response exceeded 6 months in 52% (13/25) and 12 months in 20% (5/25). Among responders, the median follow-up for DOR was 6.5 months (range: 3.0+, 23.5+ months).

Safety: The safety of denileukin diftitox was evaluated in 119 patients with relapsed or refractory Stage I-IV CTCL across three clinical trials. Patients received treatment with denileukin diftitox 9 mcg/kg daily from Day 1 through Day 5 of each 21-day cycle. Treatment was administered until disease progression or unacceptable toxicity. The median number of cycles was 5 (range: 1 to 42), with 13% exposed for 6 months or longer. Serious adverse events (SAEs) occurred in 38% of patients, most often from capillary leak syndrome, infusion-related reaction, or sepsis. Adverse events (AEs) leading to treatment discontinuation occurred in 15% of patients, treatment interruption in 33%, and dose reductions in 4%. The most common reasons for treatment modification were capillary leak syndrome and infusion-related reaction. A fatal AE of capillary leak syndrome occurred in 1 patient. The most common ($\geq 20\%$) adverse events, including laboratory abnormalities, were increased transaminases (70%), albumin decreased (53%), nausea (40%), edema (35%), hemoglobin decreased (34%), fatigue (30%), musculoskeletal pain (26%), rash (23%), chills (22%), constipation (22%), pyrexia (21%), and capillary leak syndrome (20%).

Overall benefit-risk assessment: Based on ORR and durability, denileukin diftitox has demonstrated meaningful clinical activity in this patient population, along with an acceptable safety profile to support the following indication:

- The treatment of patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

However, the overall benefit-risk is not favorable for denileukin diftitox and the review team recommends a complete response for this application. The recommendation of a complete response is based on multiple product quality deficiencies that were identified and not adequately addressed during the BLA assessment period. The main product quality issues include:

1. There is no appropriate assay for endotoxin level measurement and a lack of controls for endotoxin testing (b) (4) drug substance (DS) and drug product (DP) release (b) (4)
2. Inadequate information demonstrating sufficient knowledge of and direct control over the manufacturing process.
3. Insufficient sterilization validation data for contact materials used in DP manufacturing.
4. Insufficient data to support adequacy of the DS bioburden control strategy and bioburden method.
5. Insufficient data to support the Reference Standard qualification and requalification protocols.
6. Insufficient data for validation of the DP batch range.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CTCL includes mycosis fungoides (MF) and Sezary syndrome (SS) as well as other CD30+ lymphoproliferative disorders. • CTCL has a significant pervasive impact on quality of life due to disease manifestations including disfiguring skin lesions, intractable pruritus, recurrent infections, sleep disturbance and psychosocial problems. • Despite responses to available systemic therapies, most patients develop resistance to therapy and experience relapsed or progressive disease.	• CTCL is a serious and life-threatening condition.

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Treatment options for relapsed or refractory CTCL include retinoids, methotrexate, interferons, histone deacetylase (HDAC) inhibitors (e.g., vorinostat and romidepsin), brentuximab vedotin, mogamulizumab-kpkc, or cytotoxic chemotherapy. Allogeneic hematopoietic stem cell transplant remains the only potentially curative option, but only a small percentage of patients with CTCL are eligible and the procedure carries significant risks.	More safe and effective treatment options are needed for patients with relapsed or refractory CTCL.
Benefit	- In a single-arm trial of denileukin diftitox monotherapy in 69 patients with relapsed or refractory Stage I-III CTCL treated with 9 mcg/kg daily from Day 1 to Day 5 of each 21-day cycle, the IRC-assessed ORR was 36.2% (95% CI: 25.0, 48.7) and the CR and PR rate were 9% and 27% respectively according to the Olsen (2011) criteria. - In the 25 patients who achieved a response, the duration of response exceeded 6 months in 52% (13/25) and 12 months in 20% (5/25). - Among responders, the median follow-up for duration of response was 6.5 months (range 3.5+, 23.5+).	Based on an evaluation of response rate and duration of response, denileukin diftitox has clinically meaningful activity in patients with relapsed or refractory CTCL.
Risk and Risk Management	- In 119 patients with CTCL treated at the 9 mcg/kg daily dose, the most common AEs (incidence $\geq$ 20%), including laboratory abnormalities, were increased transaminases, hypoalbuminemia, nausea, edema, anemia, fatigue, musculoskeletal pain, rash, chills, constipation, pyrexia, and capillary leak syndrome. - Events of special interest with denileukin diftitox include	- The risks are acceptable in patients with relapsed or refractory CTCL who have received one prior systemic therapy. - The USPI includes a boxed warning for capillary leak syndrome and Warnings and Precautions for visual impairment,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	capillary leak syndrome, infusion-related reaction, hepatotoxicity, visual impairment, hypersensitivity, infection, rash, and thrombotic events. • Serious adverse events (SAEs) occurred in 38% of patients , most often from capillary leak syndrome, infusion-related reaction, or sepsis. • Adverse events (AEs) leading to treatment discontinuation occurred in 15% of patients, treatment interruption in 33%, and dose reductions in 4%. The most common reasons for treatment modification was capillary leak syndrome and infusion-related reaction. • A fatal AE of capillary leak syndrome occurred in 1 patient. • The key safety concerns for denileukin diftitox are capillary leak syndrome, infusion-related reactions, visual impairment, hepatotoxicity, and infection.	infusion-related reactions, and hepatotoxicity. • The USPI includes toxicity management for capillary leak syndrome, infusion-related reactions, visual impairment, hepatotoxicity, and other hematologic and non-hematologic toxicities. • The safe use of denileukin diftitox can be managed through labeling and routine clinical care.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
	☒ Patient reported outcome (PRO)	8.1.2
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Cutaneous T-cell lymphomas (CTCLs) include mycosis fungoides (MF) and Sézary syndrome (SS). MF is a mature T-cell non-Hodgkin lymphoma primarily presenting in the skin, but with potential for involvement of lymph nodes, blood and viscera. SS is an uncommon and more aggressive disease characterized by diffuse erythroderma, lymphadenopathy, and blood involvement with circulating malignant T-cells (Sézary cells) that match T-cell clones in the skin (Kim, et al., 2005; Dummer, et al., 2007).

CTCL has a significant, pervasive impact on quality of life (QOL), comparable to other debilitating conditions (Rosenberg, et al., 2020). This profoundly negative impact on QOL may be related to disease manifestations, including disfiguring skin lesions, intractable pruritis, recurrent infections, sleep disturbance, and psychosocial problems (Demierre, et al., 2006). Skin lesions are varied, and include patches, plaques, tumors, generalized erythroderma, and alopecia. Pruritus is a common and often debilitating symptom (Demierre, et al., 2006). As the disease progresses, systemic involvement and immune system dysregulation lead to an increased susceptibility to infections and secondary malignancies, specifically other lymphomas (Huang, et al., 2007). The most common sites of disseminated disease are lymph nodes, lungs, spleen, liver, and gastrointestinal tract; less commonly, the bone marrow or brain may become involved (Dummer, et al., 2007; Zinzani, et al., 2008).

The incidence of CTCL in the United States is estimated to be approximately 7.5 cases per 1 million people per year (Korgavkar, et al., 2013). The prevalence of CTCL in the United States is expected to be between 25,000 and 50,000 patients (Wong, et al., 2011) and CTCL is classified as an orphan disease.

The median age of onset of CTCL is 57 years, CTCL is rare in children and young adults, and the male:female ratio is 2:1 (Kim, et al., 2003; Ai, et al., 2014). The disease disproportionately affects African Americans; the incidence rate ratio compared with White Americans is 1.6 (95% CI: 1.3, 1.8) and studies have noted a higher mortality rate among Black than among White patients (rate ratio 2.4; Hinds and Heald, 2009).

Patients with Stage IA/IIA disease have the best long-term survival prognosis, with Stage IA patients having a prognosis similar to that of the age-matched general population. However, 20 to 25% of patients with early-stage disease progress to more advanced disease (Benton, et al., 2013; Gilson, et al., 2019). Patients with early-stage disease can exhibit significant blood involvement, which is associated with a poorer prognosis compared with patients without

blood involvement. Advanced skin disease and overall clinical stage, increased age, and male sex are associated with reduced survival and increased risk of disease progression. Median survival in patients with Stage IA-IIA disease was at least 15 years, with Stage IIB-IIIB was 3.4 to 4.7 years, with Stage IVB was 1.4 years, and with SS was 3.1 years (Agar, et al., 2010).

The FDA's Assessment:

The FDA agrees with the Applicant's overall assessment of the condition.

2.2 Analysis of Current Treatment Options

For CTCL, the goals of therapy are to improve or clear lesions and to control symptoms across all affected disease compartments (skin, blood, lymph nodes, and viscera), to minimize the risk of progression and to avoid treatment-related toxicity. Treatment for CTCL is individualized and specific to each person depending on the symptoms and stage of the disease (PDQ Mycosis Fungoides-Sezary Syndrome, 2022; Trautinger, et al 2017).

Patients with Stage IA-IIA MF are treated primarily with skin-directed therapies, while those with treatment-resistant early-stage MF, advanced-stage MF, or SS require systemic drugs, such as retinoids, methotrexate, interferons, histone deacetylase inhibitors, brentuximab vedotin, mogamulizumab-kpkc, or cytotoxic chemotherapy (Talpur, et al 2012; Scarisbrick, et al 2015). Most patients develop resistance to therapy and experience relapsed or progressive disease. While there are several available approved systemic therapies, current guidelines do not provide a preferred sequence or combination of therapies (NCCN, 2022). The choice of therapy for patients with persistent or recurrent CTCL is often guided by individual disease status, prior therapies received, and the experience of the treating clinician.

The systemic options for management of advanced disease generally have a limited durability of response (PDQ Mycosis Fungoides-Sezary Syndrome, 2022). In a retrospective study of 198 patients, the median time to next treatment (TTNT) was 3.9 months for single- or multi-agent chemotherapy, 8.7 months for α -interferon, and 4.5 months for HDAC inhibitors (Hughes, et al 2015). Other studies have shown longer durations of response, though the endpoints differed. Two pivotal single-arm Phase 2 studies of romidepsin reported an objective response rate of 34% (in both studies) with a median duration of response of 14 to 15 months (Piekarz, et al 2009; Whittaker, et al 2010). In a randomized, controlled Phase 3 trial of mogamulizumab-kpkc vs. vorinostat (Kim, et al 2018), the median progression-free survival (PFS) was 7.7 months for mogamulizumab-kpkc and 3.1 months for vorinostat. The longest duration of anticancer activity was reported in patients with CD30-positive MF (a subset of MF patients) or primary cutaneous anaplastic large-cell lymphoma (ALCL) treated with brentuximab vedotin, with a median PFS of 16.7 months (Horwitz, et al 2021).

Patients with CTCL often receive several therapies in sequence, when the development of resistance or intolerance requires a change to the next unique treatment. Systemic agents also

have a risk of cumulative toxicity (e.g., brentuximab vedotin and peripheral neuropathy; romidepsin and secondary cytopenias). The only potentially curative option remains allogeneic hematopoietic stem cell transplant (Dumont, et al 2020; NCCN 2022).

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication					
Product Name Product Class	Relevant Indication	Year and Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues Other Comments
FDA Approved Treatments					
Mogamulizumab- kpkc CCR4-directed mAb	adult patients with relapsed or refractory MF or SS after at least one prior systemic therapy	2018	1 mg/kg IV infusion over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity	Open label, randomized Trial: 57% MF, 43% SS Mogamulizumab n = 186 vs vorinostat n = 186 Primary endpoint investigator- assessed PFS 6.7 months (95% CI: 5.6 to 9.4) vs vorinostat 3.8 months (95% CI: 3.0 to 4.7) PFS HR 0.53 (0.41, 0.69); p<.001 ORR 28.0 % vs vorinostat 4.8% DOR 13.9 months (95% CI: 9.3, 18.9) vs vorinostat 9.0 months (95% CI: 4.6, NE)	Fatal and life-threatening: skin adverse reactions, including SJS and TEN; infusion reactions; infections; immune- mediated complications; complications of allogeneic HSCT after mogamulizumab: severe GVHD, steroid-refractory GVHD, transplant- related mortality.
Brentuximab vedotin CD30-directed antibody–drug conjugate	CD30-expressing MF (mycosis fungoides) or pcALCL after prior systemic therapy.	2017	1.8 mg/kg IV infusion over 30 minutes every 3 weeks	Open label, randomized trial of brentuximab vs physician’s choice (methotrexate or bexarotene) in CD30-positive MF or pcALCL. Primary endpoint ORR4 (ORR 4 months); brentuximab 56.3% (44.1, 68.4) vs physician choice 12.5% (4.4, 20.6)	Peripheral neuropathy; Anaphylaxis and infusion reactions; Hematologic toxicities; Serious infections and opportunistic infections; Tumor lysis syndrome; Increased toxicity in the presence of severe renal impairment; or moderate/severe hepatic impairment; Hepatotoxicity; PML; Serious dermatologic reactions; Embryo-fetal toxicity
Romidepsin HDAC inhibitor	CTCL after ≥1 systemic therapy	2009	14 mg/m2 infused IV over 4-hours on days 1, 8 and 15 of a 28-day cycle	ORR 34% (33/96) and 35% (25/71)	QT prolongation; thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; Fetal harm

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

Vorinostat HDAC inhibitor	Cutaneous manifestations of CTCL after 2 systemic therapies	2006	400 mg orally once daily with food	ORR 29.7% (22/74) in all stages ORR 29.5% (18/61) stage ≥IIb	Pulmonary embolism and DVT; Dose-related thrombocytopenia and anemia; GI disturbances (e.g., nausea, vomiting and diarrhea); Hyperglycemia; QT prolongation; Severe thrombocytopenia and GI bleeding; Fetal harm
Bexarotene Retinoid	Cutaneous manifestations of CTCL in patients refractory to ≥1 systemic therapy	1999	300 mg/m ² /day orally once daily with food	Two open-label historically-controlled studies. ORR 32%	Lipid abnormalities; Acute pancreatitis; Liver function test abnormalities; Hepatic insufficiency; Thyroid axis alterations; Leukopenia; Cataracts
Denileukin diftitox (ONTAK) IL-2 receptor directed fusion protein with DT fragments	Persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor	1999 ^a	9 or 18 mcg/kg/day by IV infusion over 30 to 60 minutes for 5 consecutive days every 21 days for 8 cycles	Study 1 (Stage Ia-III): Randomized, double-blind, PBO-controlled trial of ONTAK (2 doses) vs placebo in recurrent or persistent CTCL ORR 38% 9 µg; 49% 18 µg; 16% PBO. Study 2 (Stage IIb to IVa): Randomized, double blind study of ONTAK (2 doses). ORR 23% 9 µg; 36% 18 µg	Infusion reactions; Capillary leak syndrome; Loss of visual acuity and color vision; Monitor serum albumin levels
Methotrexate Antimetabolite	Alone or in combination with other anticancer agents for advanced MF (CTCL)	1959	5-50 mg orally once weekly or 15-37.5 mg orally twice weekly	ORR up to 50% as single agent	Bone marrow suppression (anemia, leukopenia, thrombocytopenia, aplastic anemia); tumor lysis syndrome; transaminase elevation, hepatic fibrosis, cirrhosis; interstitial pneumonitis, severe nephropathy; diarrhea, hemorrhagic enteritis, intestinal perforation; severe skin reactions; opportunistic infections; secondary malignancy (lymphoma). Toxicities may be fatal.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

*Accelerated approval or full approval

CTCL = cutaneous T-cell lymphoma, DOR = duration of response, DT = diphtheria toxin, HL = Hodgkin lymphoma, HDAC = histone deacetylase, HR = hazard ratio, HSCT = hematopoietic stem cell transplantation, GVHD = graft-versus-host disease, IL-2 = interleukin 2, IV = intravenous, MF = mycosis fungoides, NE = not evaluable, ORR = objective response rate, PFS = progression-free survival, SJS = Stevens-Johnson syndrome, SS = Sézary syndrome, TEN = toxic epidermal necrolysis. pcALCL = primary cutaneous anaplastic large cell lymphoma; MF = mycosis fungoides, DVT = deep vein thrombosis, GI = gastrointestinal, PML = progressive multifocal leukoencephalopathy, PBO = placebo.

The Applicant's Position:

CTCL is progressive and it is important to halt or slow disease progression as much as possible as advanced-stage disease is associated with a poor prognosis. Despite responses to currently available systemic therapies, most patients develop resistance to therapy and experience relapsed or progressive disease. There is an unmet medical need for safe and effective new therapies that can offer durable responses for patients with persistent or recurrent advanced-stage CTCL. If approved, E7777 would help to address this unmet medical need.

The FDA's Assessment:

The FDA agrees with the description of the current treatment options. Notably, Ontak (denileukin diftitox) is the same active ingredient as E7777. For additional information on the regulatory history of Ontak and E7777, see Section 3.2.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

E7777 is not currently approved or registered in the US.

E7777 received marketing approval in Japan in March 2021 under the brand name of Remitoro® for treatment of patients with relapsed or refractory CTCL or PTCL.

The FDA's Assessment:

The FDA acknowledges the Applicant's position.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

ONTAK: Denileukin diftitox (DD; ONTAK) received accelerated approval (biologics license application [BLA] 103767) in 1999 for the treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor, based on the results of the blinded, randomized, Phase 3 Study 93 04 10.

In 2008, ONTAK received full approval based on the results of the double-blind, randomized, placebo-controlled Phase 3 Study L4389-11 (Study 11).

In 2014, the manufacturing of ONTAK was discontinued due to manufacturing difficulties.

E7777: The accelerated approval of ONTAK included a requirement to improve the purification process to increase product purity. In 2009, Chemistry, Manufacturing and Controls (CMC) amendments were submitted to fulfill this requirement. In 2010, FDA stated that the product cannot be determined to be comparable to ONTAK based on quality criteria alone and that human clinical study data are required for the commercialization of the new improved purity material for the current indication.

The new improved purity material assigned a new development code (E7777) and IND 110489 was submitted in 2011 (b) (4)

(b) (4). Following discussion with FDA in 2011 and 2012, agreement was reached on a registration study in CTCL for E7777 (Study E7777-G000-302; Study 302). FDA determined that a single-arm trial of E7777 in the approved indication for ONTAK would be adequate for regular approval provided the Sponsor justifies that E7777 is safe, pure, and potent for the proposed indication. Subsequent key regulatory events are noted in Table 2.

Table 2: Summary of Key Regulatory Events submitted to E7777 IND 1104899	
Regulatory Event	Date
Type C Meeting to reach agreement on a proposed clinical study design and nonclinical data to support marketing approval for E7777 (i.e., improved purified ONTAK drug substance) for the treatment of cutaneous T-cell lymphoma (CTCL) (intended to replace ONTAK on the market).	16 Jun 2011
Type C Meeting to reach agreement on the design of Study 302, a Phase 3 trial investigating E7777 in patients with CTCL, to support approval of a BLA.	25 Oct 2011
FDA Advice issued to clarify that a single-arm trial of E7777 in the approved indication for ONTAK would be adequate for regular approval for E7777 provided that the Sponsor justify that E7777 is safe, pure, and potent for the proposed indication.	24 Jan 2012
FDA Advice issued on the protocol and study design on Study 302, including recommendations on the endpoints evaluated.	10 May 2012
Orphan drug designation granted (# 11-3413) for E7777 for the treatment of patients with persistent or recurrent CTCL	12 Jul 2013
Type C Meeting Written Responses provided feedback on the CMC and nonclinical information for inclusion in the E7777 BLA	29 Mar 2017
Type C Meeting provided feedback on control strategies for E7777 drug substance and drug product	12 Sep 2019
Type C Meeting to reach agreement on the key primary and secondary analyses for Study 302 in support of the E7777 BLA.	02 Oct 2019
Type C Meeting to discuss the development and possible requirement for a companion diagnostic for the safe and effective use of E7777	26-27 Jan 2021
Type C Meeting Written Responses relating to the analyses of data for Study 302 and proposed content and format of the BLA submission	21 Dec 2021
Initial Pediatric Study Plan agreement including full waiver from conducting pediatric studies in children from birth (0) to <17 years of age	24 Jan 2022
Type B Pre-BLA meeting to reach agreement on the totality of the clinical efficacy and safety data intended for submission in the E7777 BLA.	28 Jun 2022
Type C Meeting Written Responses (meeting cancelled) to inform and gain alignment regarding the evaluation of CD25 tumor expression should E7777 be granted marketing approval for the treatment of CTCL.	05 Jul 2022

The FDA’s Assessment:

The FDA agrees with the Applicant’s position. Importantly, given the prior regulatory approval of Ontak (same active ingredient as E7777) based on randomized data in patients with CTCL, the FDA agreed that a single-arm trial of E7777 may be used to support an application seeking regular approval. Additionally, in October 2019, the FDA also recommended development of a diagnostic for CD25 testing as it may be needed for the safe and effective use of E7777.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

OSI inspected the Applicant for quality of study conduct and oversight for Study E7777-G000-302, along with two clinical sites that were selected by the clinical team based on risk ranking in the BIMO clinical investigator site selection tool (CISST), numbers of enrolled subjects, and prior inspectional history. The clinical sites included 1. Dr. Francine Foss, Yale University School of Medicine, and 2. Dr. Madeleine Duvic, M.D. Anderson Cancer Center. No issues warranting action were identified during the review of either clinical site. The Applicant's site audit included, but were not limited to, selection, monitoring, financial disclosures of research staff, study monitoring, safety reporting, data collection and handling, records retention, and electronic records. The Applicant's oversight of the clinical trial and the quality of conducting the study were determined to be adequate. The audited study data submitted to the Agency was deemed acceptable in support of the BLA application, in compliance with Good Clinical Practice.

4.2 Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed the assessment of BLA 761312 for Lymphir (Denileukin diftitox-cxdl) manufactured by Citius Pharmaceuticals, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Lymphir is well-controlled and will lead to a product that is pure and potent. The Office of Pharmaceutical Quality is recommending a Complete Response letter be issued to Citius Pharmaceuticals, Inc. The main deficiencies are outlined below. The Applicant will need to submit additional information and data to address the issues.

Multiple product quality deficiencies were identified and were not adequately addressed during the BLA assessment period. There is no appropriate assay for endotoxin level measurement and lack of controls for endotoxin testing on (b) (4) drug substance (DS) and drug product (DP) release (b) (4)

There was also a lack of information demonstrating that the Applicant has sufficient knowledge of and direct control over the manufacturing process. Additional issues identified include insufficient sterilization validation data for contact materials used in DP manufacturing, insufficient data to support adequacy of the DS bioburden control strategy and bioburden method, insufficient data to support the Reference Standard qualification and requalification protocols, and insufficient data for validation of the DP batch range.

4.3 Clinical Microbiology

See information provided in Section 4.2.

4.4 Devices and Companion Diagnostic Issues

During a Type C Meeting in October 2019, the FDA recommended development of a diagnostic for CD25 testing as it may be necessary for the safe and effective use of E7777 and warrant a companion diagnostic (CDx). (b) (4)

(b) (4)

In the FDA's review of the available data and CTCL disease background, CD25 is not a marker for diagnosis of CTCL and its presence does not derive clinical decision making in clinical practice. For the historical Study 11 of Ontak, the Applicant used CD25 screening as a tool for identifying patients who might respond to denileukin diftitox. Patients with high CD25 expression (> 20% CD25 expression) were assumed to express the high-affinity IL-2 receptor necessary for response to denileukin diftitox, whereas patients with skin lesions exhibiting < 20% CD25 expression were presumed to be unresponsive to denileukin diftitox. As additional post-marketing studies of Ontak were completed, the findings suggested that CD25 low expression does not preclude a meaningful clinical response to Ontak in patients with CTCL. Supporting evidence includes that 1) intermediate IL-2R can also cause internalization and signal transduction despite not expressing CD25, 2) the 20% cut off for CD25 expression is arbitrary, 3) the IHC assay is technically challenging and results can vary substantially, 4) CD25 expression can be variable at different tumor sites within the same patient, and 5) responses have been demonstrated across different levels of CD25 expression. In Study 302, no major differences in CD25 expression level were observed between responders and nonresponders (see Section 8.1.2 for response data by CD25 expression). Based these findings and the rationale outlined above, the FDA concluded that no companion diagnostic for CD25 is needed for the safe and effective use of E7777. (b) (4)

(b) (4)

See Section 5.1 regarding the updated established pharmacologic class (EPC) for E7777 that was made in response to the evaluation of CD25 as a biomarker and the mechanism of action of E7777 and the IL-2 receptor.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Denileukin diftitox (DD), an IL-2-receptor-directed cytotoxin, is a recombinant DNA-derived fusion protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met1-Thr387)-His and the sequence for human interleukin-2 (IL-2; Ala1-Thr133). DD is designed to direct the cytotoxic action of diphtheria toxin (DT) to cells which express the IL-2 receptor (IL-2R) for the treatment of adult patients with relapsed or refractory stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy. Once DD internalizes into the cell, the DT fragment is cleaved and the free DT fragments inhibit protein synthesis, resulting in cell death. E7777 has the same active component as ONTAK but has an improved purity profile and greater potency as a result of higher active monomer content relative to ONTAK (for the regulatory history of ONTAK to E7777, see Section 3.2). The nonclinical development program for DD included various in vitro and in vivo studies to evaluate the pharmacology, bridging pharmacokinetic studies to compare E7272 (ONTAK) and E7777, general toxicology studies, and the weight-of-evidence (WoE) assessment of the risk for reproductive and developmental toxicity.

The nonclinical pharmacology of DD has been well characterized and reviewed in the BLA for ONTAK. To support the current BLA, the pharmacology studies focused on determining the role of DD in regulatory T lymphocyte (Treg) depletion and evaluating the in vivo antitumor activity in mouse isograft models. The in vitro studies were conducted to demonstrate the effect of E7272 on the depletion of Treg in human peripheral blood mononuclear cells (PBMC) and murine splenocytes with concentrations ranging 33 - 2700 ng/mL and 10 - 3000 ng/mL, respectively. In the in vivo mouse isograft models, intravenous administration of E7777 showed antitumor activity against cancer cells in immunocompetent mice, but had no effect in nude mice lacking T cells. The antitumor activity of E7777 in combination with an anti-PD-1 antibody against cancer cells showed an increased tumor growth inhibition compared to each monotherapy.

Comparative pharmacokinetic (PK) studies were conducted in rats to bridge E7777 to the existing nonclinical data acquired using DD manufactured as ONTAK (E7272). A repeat-dose of either E7272 or E7777 at 40.53 µg/kg/day showed a generally similar result for AUC when analyzed by enzyme-linked immunosorbent assay (ELISA). The C_0 (extrapolated concentration at time t=0) values in male rats were 1.51 - 2.09-fold higher in E7777 relative to E7272. When serum concentrations were analyzed by bioassay, there were higher C_0 (1.69-fold) and AUC (3.29-fold) values for E7777 relative to E7272 in the male rats. In female rats, E7777 also showed higher C_0 (1.39-fold) and AUC (2.29-fold) values relative to E7272. The AUC on Day 29 was lower than that of Day 1 for both E7777 and E7272 in rats, indicating an anti-DD antibody

generation. Overall, E7777 resulted in higher systemic exposure to DD in comparison to E7272 in rats.

Two repeat-dose studies in rats were conducted to assess the general toxicology of E7777: a 6-week study to compare E7777 with E7272 and a 14-week study with E7777. The product was administered in rats via intravenous administration, which is consistent with the intended clinical route of administration. Overall, adverse findings included systemic inflammatory responses in multiple organs, and toxicities in the liver, kidney, and hematopoietic system. In the 6-week study, E7777 was administered to rats at doses of 2, 10, or 40 µg/kg and E7272 was given to a separate group of rats at 40 µg/kg. A total of two unscheduled deaths and six moribund euthanasias occurred in the E7777-treated high-dose (HD) group. Adverse E7777-related clinical observations included decreased activity, increased porphyrin staining, altered fecal consistency, hunched posture and cold to touch. Toxicities included decreased body weight gain and food consumption, lymphopenia, neutrophilia, alterations in hepatic and renal function, lymphoid/eosinophilic tissue infiltration, and adrenocortical vacuolation. E7272 administration caused a similar toxicity profile but with comparatively less severe changes. In the 14-week study, E7777 was administered to rats at doses of 2, 10, or 20 µg/kg. A total of two E7777-related moribund euthanasias occurred in the HD group. The changes in this study were comparable in severity and nature with those in the 6-week study including decreased body weight gain and food consumption, neutrophilia, toxicities in the liver and kidney, lymphocytic/eosinophilic infiltration, and effects on the parenchyma. Microscopic findings were observed in the kidney (regeneration of the renal tubule), male reproductive organs (seminiferous tubule, epididymis, prostate, and seminal vesicle), and bone marrow (femur and sternum).

While no animal studies were conducted to assess the reproductive and developmental risks of DD, a WoE-based risk assessment report was submitted. The assessment is based on the immune system-mediated toxicities due to the depletion of regulatory Treg. Based on the product's mechanism of action and pharmacodynamic effects, DD can cause depletion of Treg, which is important for immune tolerance in pregnancy, protecting the fetus from the maternal immune response. Tregs are also known to play a role in placental development and the maintenance of pregnancy. Insufficient Treg numbers or inadequate functional competence have been implicated in infertility, recurrent miscarriage, and placental insufficiency causing preeclampsia, fetal growth restriction, and excessive inflammation in the uterus and gestational tissues. The recommendation for using contraception in females of reproductive potential for 7 days after the last dose of DD, as reflected in the product label, is based on 5 half-lives of the drug product.

The current established pharmacological class (EPC) for DD based on the ONTAK label is "CD25-directed cytotoxin" and the indication is for the treatment of patients with persistent or

recurrent cutaneous T-cell lymphoma (CTCL) (b) (4), whose malignant cells express the CD25 component of the IL-2 receptor. Based on the rationale that DD is not specific for CD25 and the expression level of CD25 does not correlate with a clinical response to ONTAK, alternative language for the EPC and indication has been proposed: “BRAND NAME is an IL-2-receptor-directed cytotoxin indicated for the treatment of adult patients with relapsed or refractory stage I-III CTCL after at least one prior systemic therapy”.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of DD for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant’s Position:

BLA 103767 (ONTAK; E7272): Studies characterizing the pharmacology/pharmacodynamics (PD), metabolism/pharmacokinetics (PK), and toxicology of DD. As discussed previously with the Agency, the Applicant is cross-referencing the nonclinical summaries and nonclinical data submitted in ONTAK BLA 103767 in support of the E7777 BLA.

IND 110489 (E7777): Two rat bridging PK studies, one comparative 3-cycle intravenous (IV) Good Laboratory Practice (GLP) rat toxicity study to bridge to the existing nonclinical ONTAK data, and pharmacology studies with DD to determine the role of immunosuppressive regulatory T-lymphocytes (Treg) depletion in the drug’s antitumor activity.

BLA 761312 (E7777): Subsequent to IND 110489, a 14-week intermittent IV dose toxicity study with E7777 in rats was conducted. All nonclinical data contained in and subsequent to E7777 IND 110489 are included in BLA 761312.

CMC: DMF (b) (4); DMF (b) (4); BB-MF (b) (4); DMF (b) (4); DMF (b) (4)

5.3 Pharmacology

Primary pharmacology

The Applicant’s Position:

Cytotoxic activity of DD in vitro was characterized in human tumor IL-2 receptor-expressing cell lines and in activated human peripheral blood mononuclear cells (PBMC), where half maximal inhibitory concentration (IC₅₀) ranged from 0.1 to 12 ng/mL. In vivo antitumor activity was demonstrated in a CP3 murine model of IL-2 receptor-expressing malignancy under different dosing schedules. DD caused selective depletion of the Treg population in human PBMCs and murine splenocytes in vitro. DD also inhibited the immunosuppressive function of Tregs toward CD4⁺ T-cells, suggesting that DD had cytotoxic action on Tregs. In vivo DD inhibited growth of

implanted colon tumor isografts (which do not express the IL-2 receptor) in normal mice but had no effect in mice lacking T-cells, supporting the conclusion that DD exerts antineoplastic activity through inhibition of IL-2 receptor-expressing T-cells, such as Tregs. DD also inhibits growth of isografts of murine B16F10 melanoma, a tumor shown to be susceptible to Treg depletion in a mouse model.

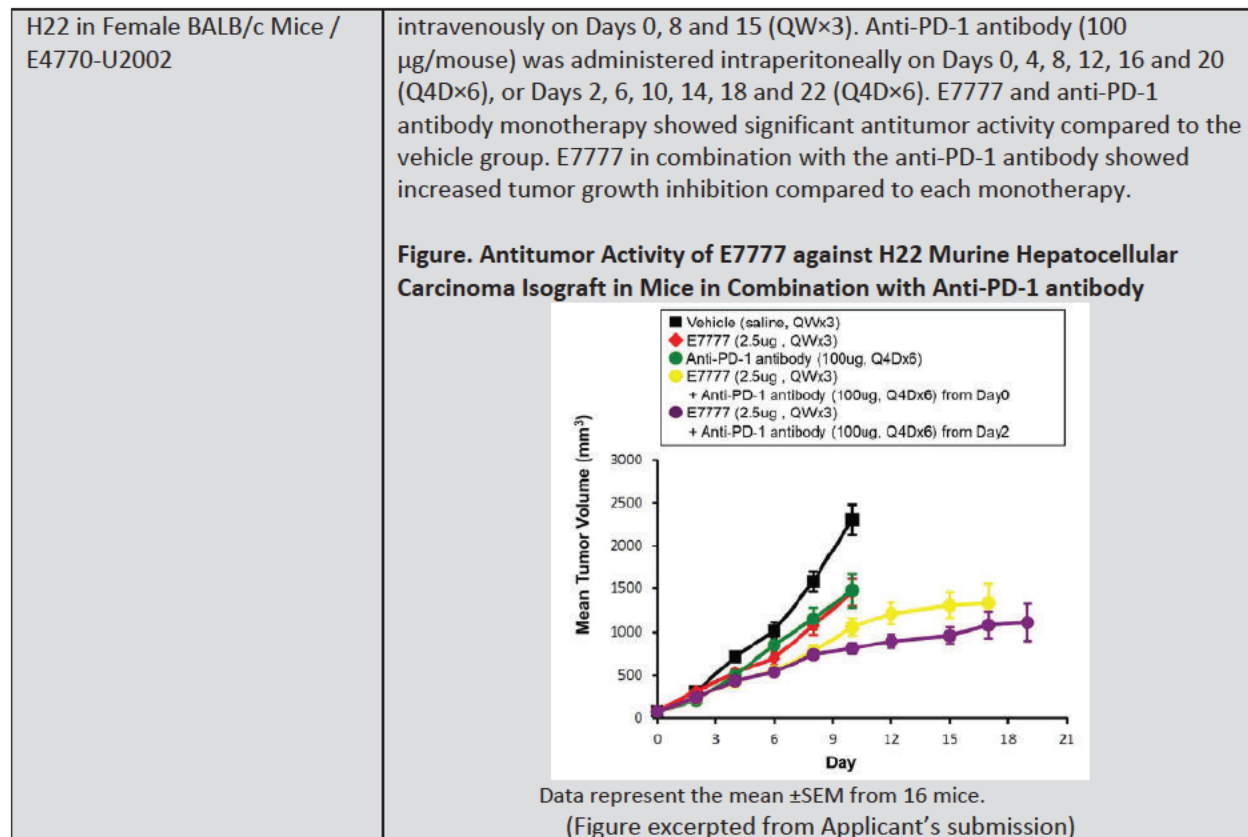
Further, the combination of DD with an anti-programmed cell death protein 1 (PD-1) antibody, an immune checkpoint inhibitor (ICI), showed greater tumor growth inhibition than each monotherapy in CT26 and H22 isograft models. It has been reported that Tregs are involved in the mechanisms of resistance to ICIs, therefore, the depletion of Tregs with DD might enhance cancer immunity by ICIs.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Study Title/Study No.	Findings
Effect of in vitro exposure to ONTAK on human peripheral blood regulatory T lymphocyte populations / PPC-2008-06N	The effects of E7272 on Tregs (CD3 ⁺ CD4 ⁺ CD25 ⁺ FOXP3 ⁺) were evaluated by measuring the levels of the Treg population in human PBMCs. A 2-hour exposure to 0.33 - 2.7 µg/mL of E7272 caused a depletion of Treg cells in a concentration-dependent manner and no effect on CD3 ⁺ CD4 ⁺ T cells. These results suggest that E7272 selectively killed human Treg cells in PBMCs.
Effect of in vitro exposure to ONTAK on murine splenocyte regulatory T lymphocyte populations / PPC-2008-04N	The effects of E7272 on murine Tregs were evaluated by measuring the levels of the Treg population in murine splenocytes. A 1-hour exposure to 10 - 3000 ng/mL of E7272 caused a depletion of Treg cells in a concentration-dependent manner and no effect on CD4 ⁺ CD25 ⁻ T cells. These results suggest that E7272 selectively killed murine Treg cells in the murine splenocyte population.
Evaluation of The Antitumor Efficacy of ONTAK Against Subcutaneous CT26 Murine Colon Tumor Isografts / PPC-2008-07N, PPC2008-08N	The antitumor activity of E7272 in vivo was evaluated using a CT26 murine colorectal carcinoma isograft in female BALB/c mice and female athymic mice. CT26 cells were implanted subcutaneously into the mice and the animals were dosed with E7272 intravenously once per week for two weeks (Q7D×2) at 0, 3, or 4.5 µg/mouse for BALB/c mice and 4.5 µg/mouse for athymic mice. Treatment of E7272 resulted in a dose-dependent inhibition of tumor growth in BALB/c mice, whereas no effect was observed in athymic mice. These results suggest that the activity of E7272 is dependent upon the presence of T cells, which athymic mice lack.

	Figure. Antitumor Activity of Denileukin Diftitox against CT26 Murine Colorectal Carcinoma Isograft in Normal and Athymic Mice A: BALB/c mice, B: athymic mice. Data represent the mean $\pm$SEM from 10 mice. E7272 = denileukin diftitox manufactured with the process used for ONTAK. (Figure excerpted from Applicant's submission)
In Vivo Efficacy Study of E7777 and Anti-PD-1 in the Treatment of Subcutaneous Murine Colorectal Cancer Model CT26 in Female BALB/c Mice / E4770-U2002	The antitumor activity of E7777 as a monotherapy or in combination with an anti-PD-1 antibody was evaluated using a CT26 isograft in BALB/c mice. E7777 (2.5 μg/mouse) was administered intravenously on Days 0, 8 and 15 (QW$\times$3). Anti-PD-1 antibody (100 μg/mouse) was administered intraperitoneally on Days 0, 4, 8, 12, 16 and 20 (Q4D$\times$6), or Days 2, 6, 10, 14, 18 and 22 (Q4D$\times$6). E7777 and anti-PD-1 antibody monotherapy showed a slight antitumor activity compared to the vehicle control without statistical significance; however, E7777 in combination with the anti-PD-1 antibody showed increased tumor growth inhibition compared to each monotherapy. Figure. Antitumor Activity of E7777 against CT26 Murine Colorectal Carcinoma Isograft in Mice in Combination with Anti-PD-1 antibody Data represent the mean $\pm$SEM from 16 mice. E7777 = denileukin diftitox manufactured with improved downstream process compared to ONTAK. Q4D$\times$6 = once every 4 days 6 times, QW$\times$3 = once a week 3 times. (Figure excerpted from Applicant's submission)
In Vivo Efficacy Study of E7777 and Anti-PD-1 in the Treatment of Subcutaneous Murine Liver Cancer Model	The antitumor activity of E7777 as a monotherapy or in combination with an anti-PD-1 antibody was evaluated using a H22 murine hepatocellular carcinoma isograft in BALB/c mice. E7777 (2.5 μg/mouse) was administered



Secondary Pharmacology

The Applicant's Position:

No specific secondary pharmacology studies were conducted.

The FDA's Assessment:

The FDA concurs with the Applicant.

Safety Pharmacology

The Applicant's Position:

The safety pharmacology assessment conducted with DD (as E7272), including the effects on cardiovascular (CV), respiratory, and renal function were previously described in BLA 103767. No clinically significant changes in blood pressure, heart rate, vascular permeability, or blood cytokine levels were observed. A decrease in glomerular filtration rate accompanied by a slight decrease in renal plasma flow was observed following 10 days of DD administration. These changes appeared to be related to alterations in renal hemodynamics rather than due to direct toxicity.

The FDA's Assessment:

The FDA concurs with the Applicant.

5.4 ADME/PK

The Applicant's Position:

After a single E7777 or E7272 administration, serum levels of DD were dose proportional and DD did not accumulate with repeated dosing in rats and monkeys. In rats, the liver and kidneys were the primary sites of radiolabeled-DD distribution. DD was metabolized by proteolytic degradation. Excreted material was less than 25% of the total injected dose and consisted of low molecular weight break-down products. In a single-dose PK study in rats, no difference was observed in serum exposure of DD after E7777 or E7272 administration, as measured by enzyme-linked immunosorbent assay (ELISA). When serum concentrations were assessed by bioassay, the mean extrapolated initial concentration and mean area under the concentration time curve (AUC) over 2 hours following E7777 administration were increased 1.96 and 1.33-fold, respectively, relative to those following E7272 administration. In a repeat dose study in male and female rats, ELISA results showed no difference in AUC of DD after E7777 or E7272 administration in female rats. The bioassay results indicated a 1.58 to 2.85-fold increase in AUCs of DD following E7777 administration across male and female rats, relative to those following E7272 administration. The AUCs were lower after the final dose than those of Day 1 following E7777 or E7272 administration in male and female rats from both ELISA and bioassay results. Rats that confirmed positive for immunogenicity showed decreased final dose AUC relative to Day 1.

The FDA's Assessment:

The FDA agrees with the Applicant's summary for the ADME/PK assessment. Additional details are provided in the review below.

A single-dose PK study was conducted in male rats to compare the PK of E7272 and E7777 (Study No. DMPKAP2010-052). After a single 40 µg/kg IV administration of E7272 or E7777, the serum samples were analyzed using an ELISA and a cell-based bioassay to determine the levels of ONTAK-equivalents and bioactivity, respectively. The PK analysis of E7272 and E7777 by ELISA indicated no apparent differences in C₀ and AUC values. When the samples were analyzed by bioassay, E7777 administration resulted in higher C₀ and AUC values 1.96-fold and 1.33-fold, respectively, the values for E7272 administration. In a repeat-dose PK study in rats, the animals were administered either E7272 or E7777 at 40.53 µg/kg for 3 continuous cycles, each consisting of a 5-day treatment period followed by a 9-day non-dosing period, with the exception of the 3rd cycle consisting of only 1 dosing day (Study No. DMPKAP2010-063). The PK analysis by ELISA showed generally similar results for AUC after E7777 or E7272 administration.

The C₀ values in male rats were 1.51-2.09-fold higher for E7777 relative to E7272. The bioassay results showed higher C₀ (1.69-fold) and AUC (3.29-fold) values for E7777 relative to E7272 in the male rats. In the female rats, E7777 administration also resulted in higher C₀ (1.39-fold) and AUC (2.29-fold) values relative to E7272. The AUC on Day 29 was lower than that of Day 1 for both E7777 and E7272 using both assay methods, indicating anti-DD antibody generation. Overall, E7777 resulted in higher C₀ and AUC values in comparison to E7272.

Type of Study	Major Findings																																																																																						
Pharmacokinetics of E7272 (Improved Process Batch versus Commercial Batch) After Intravenous Administrations in Male Sprague Dawley Rats / DMPKAP2010-052	Table. PK Parameters of DD After a Single IV Dose to Male Rats <table border="1"> <thead> <tr> <th rowspan="2">Dosed Material</th> <th colspan="2">E7777</th> <th colspan="2">E7272</th> </tr> <tr> <th>ELISA</th> <th>Bioassay</th> <th>ELISA</th> <th>Bioassay</th> </tr> </thead> <tbody> <tr> <td colspan="5">PK parameters</td> </tr> <tr> <td>C₀ (ng/mL)</td> <td>977±172</td> <td>929±404</td> <td>1041±515</td> <td>474±158</td> </tr> <tr> <td>AUC_(0-inf) (ng•h/mL)</td> <td>627±76</td> <td>NA^a</td> <td>654±108</td> <td>NA^a</td> </tr> <tr> <td>AUC_(0-2h) (ng•h/mL)</td> <td>571±55</td> <td>385±142</td> <td>560±89</td> <td>290±100</td> </tr> <tr> <td>CL (mL/h/kg)</td> <td>64.6±7.7</td> <td>101.2±41.7</td> <td>63.0±12.7</td> <td>168.2±81.7</td> </tr> <tr> <td>V_{ss} (mL/kg)</td> <td>49.0±6.0</td> <td>75.5±26.1</td> <td>60.5±13.9</td> <td>121.8±24.9</td> </tr> <tr> <td>t_{1/2} (h)</td> <td>0.61±0.10</td> <td>0.70±0.39</td> <td>0.80±0.20</td> <td>0.65±0.32</td> </tr> </tbody> </table> Each parameter represents mean ±SD of 5 to 9 animals. AUC_(0-inf) = area under the concentration time curve from zero time extrapolated to infinite time, C₀ = extrapolated concentration at time t=0. CL = total serum clearance. NA = not applicable. t_{1/2} = terminal elimination phase half-life, V_{ss} = volume of distribution at steady state. a: Due to >20% extrapolation, AUC_(0-inf) was considered not reliable. (Table excerpted from Applicant's submission)	Dosed Material	E7777		E7272		ELISA	Bioassay	ELISA	Bioassay	PK parameters					C ₀ (ng/mL)	977±172	929±404	1041±515	474±158	AUC _(0-inf) (ng•h/mL)	627±76	NA ^a	654±108	NA ^a	AUC _(0-2h) (ng•h/mL)	571±55	385±142	560±89	290±100	CL (mL/h/kg)	64.6±7.7	101.2±41.7	63.0±12.7	168.2±81.7	V _{ss} (mL/kg)	49.0±6.0	75.5±26.1	60.5±13.9	121.8±24.9	t _{1/2} (h)	0.61±0.10	0.70±0.39	0.80±0.20	0.65±0.32																																										
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E7272: A 4-Week Intravenous Injection Pharmacokinetic Study in Rats / DMPKAP2010-063	Table. PK Parameters of DD in the 4-Week Intermittent IV Dose in Rats <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th rowspan="2">Study Day</th> <th colspan="2">E7777</th> <th colspan="2">E7272</th> </tr> <tr> <th>ELISA</th> <th>Bioassay</th> <th>ELISA</th> <th>Bioassay</th> </tr> </thead> <tbody> <tr> <td colspan="6">Males</td> </tr> <tr> <td rowspan="3">C₀ (ng/mL)</td> <td>Day 1</td> <td>1165±207</td> <td>1463±671</td> <td>771±183</td> <td>587±228</td> </tr> <tr> <td>Day 5</td> <td>1189±386</td> <td>1568±1430</td> <td>568±91</td> <td>477±222</td> </tr> <tr> <td>Day 29</td> <td>2079^a</td> <td>1527±490</td> <td>1130±211</td> <td>678±254</td> </tr> <tr> <td rowspan="3">AUC_(0-inf) (ng•h/mL)</td> <td>Day 1</td> <td>852±142</td> <td>687±137</td> <td>760±138</td> <td>253±60</td> </tr> <tr> <td>Day 5</td> <td>806±238</td> <td>632±206</td> <td>662±165</td> <td>375±98</td> </tr> <tr> <td>Day 29</td> <td>731^a</td> <td>665±137</td> <td>640±141</td> <td>233±34</td> </tr> <tr> <td colspan="6">Females</td> </tr> <tr> <td rowspan="3">C₀ (ng/mL)</td> <td>Day 1</td> <td>1248±299</td> <td>1357±531</td> <td>1156±629</td> <td>875±394</td> </tr> <tr> <td>Day 5</td> <td>946±408</td> <td>1079±358</td> <td>981±290</td> <td>774±311</td> </tr> <tr> <td>Day 29</td> <td>1421±480</td> <td>810±437</td> <td>1151±436</td> <td>354^a</td> </tr> <tr> <td rowspan="3">AUC_(0-inf) (ng•h/mL)</td> <td>Day 1</td> <td>716±67</td> <td>516±160</td> <td>761±282</td> <td>297±107</td> </tr> <tr> <td>Day 5</td> <td>645±208</td> <td>622±181</td> <td>850±204</td> <td>359±114</td> </tr> <tr> <td>Day 29</td> <td>648±261</td> <td>315±164</td> <td>501±132</td> <td>200^a</td> </tr> </tbody> </table> Each parameter represents mean ±SD of 3 to 7 animals except where indicated. a: mean of 2 animals. (Table excerpted from Applicant's submission)	Parameter	Study Day	E7777		E7272		ELISA	Bioassay	ELISA	Bioassay	Males						C ₀ (ng/mL)	Day 1	1165±207	1463±671	771±183	587±228	Day 5	1189±386	1568±1430	568±91	477±222	Day 29	2079 ^a	1527±490	1130±211	678±254	AUC _(0-inf) (ng•h/mL)	Day 1	852±142	687±137	760±138	253±60	Day 5	806±238	632±206	662±165	375±98	Day 29	731 ^a	665±137	640±141	233±34	Females						C ₀ (ng/mL)	Day 1	1248±299	1357±531	1156±629	875±394	Day 5	946±408	1079±358	981±290	774±311	Day 29	1421±480	810±437	1151±436	354 ^a	AUC _(0-inf) (ng•h/mL)	Day 1	716±67	516±160	761±282	297±107	Day 5	645±208	622±181	850±204	359±114	Day 29	648±261	315±164	501±132	200 ^a
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		ELISA	Bioassay	ELISA	Bioassay																																																																																		
Males																																																																																							
C ₀ (ng/mL)	Day 1	1165±207	1463±671	771±183	587±228																																																																																		
	Day 5	1189±386	1568±1430	568±91	477±222																																																																																		
	Day 29	2079 ^a	1527±490	1130±211	678±254																																																																																		
AUC _(0-inf) (ng•h/mL)	Day 1	852±142	687±137	760±138	253±60																																																																																		
	Day 5	806±238	632±206	662±165	375±98																																																																																		
	Day 29	731 ^a	665±137	640±141	233±34																																																																																		
Females																																																																																							
C ₀ (ng/mL)	Day 1	1248±299	1357±531	1156±629	875±394																																																																																		
	Day 5	946±408	1079±358	981±290	774±311																																																																																		
	Day 29	1421±480	810±437	1151±436	354 ^a																																																																																		
AUC _(0-inf) (ng•h/mL)	Day 1	716±67	516±160	761±282	297±107																																																																																		
	Day 5	645±208	622±181	850±204	359±114																																																																																		
	Day 29	648±261	315±164	501±132	200 ^a																																																																																		

5.5 Toxicology

5.5.1. General Toxicology

The Applicant's Position:

The toxicologic profile of E7777 was based on the following: E7272 toxicology data summarized in BLA 103767, and 3-and 7-cycle repeated-dose toxicity studies in rats using E7272 and/or E7777. The species used in the toxicologic assessment were relevant pharmacologically

because mitogen-activated cells freshly isolated from monkey, mouse, and rat are all sensitive to the action of DD as detailed in BLA 103767. In a 6-week (3-cycle) intermittent dose toxicity study in rats, conducted to compare E7777 with E7272, adverse effects consisted of decreased body weight gain and food consumption, lymphopenia, neutrophilia, alteration of liver and renal function parameters, lymphocytic/eosinophilic tissue infiltration, and adrenocortical vacuolation. The incidence and severity of these changes was dose-dependent and generally reversible. E7272 administration caused similar but non-life-threatening effects, consistent with what has been reported previously. From a toxicologic perspective, E7777 and E7272 are similar qualitatively, and there was no difference in their toxicity profiles. E7777 is manufactured with an improved process that produces a higher proportion of active monomer in the finished product. The increase in bioactivity per milligram protein for E7777 has been confirmed in vitro and in vivo. Quantitatively, the differences in toxicologic profile can be attributed to differences in potency between E7777 and E7272, mainly due to increased monomer content. In a 14-week (7-cycle) toxicity study of E7777 in rats, toxicologic findings similar to those noted in the 3-cycle study were observed, but no exaggerated changes were observed following longer-term administration. A reduction in exposure and toxicity of E7777 was observed possibly due to the production of anti-drug antibodies.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment; see additional information provided below for the 6-week and 13-week repeat-dose toxicity studies in rats.

E7272: A 6-Week Intermittent Intravenous Toxicity Study in Rats/1010-0351

- There were 2 unscheduled deaths and 6 moribund euthanasias in the E7777-treated high-dose group; the deaths of the animals were considered E7777-related. The animals exhibited decreased body weight, decreased activity, increased porphyrin staining, altered fecal consistency, hunched posture and cold to touch.
- The hematological findings included neutrophilia, lymphopenia, and decreased red blood cell parameters in the E7777-treated high-dose group. Similar, but less severe changes were observed in the E7272-treated group as expected with the exposure to E7777 approximately two times that of E7272.
- The main findings include lymphocytic/eosinophilic tissue infiltration, adrenocortical vacuolation and alterations in liver and renal function parameters.

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2, 10, or 40 µg/kg/day of E7777 for 3 cycles; each cycle consisted of a 5-day on followed by a

Route of administration:
Formulation/Vehicle:
Species/Strain:
Number/Sex/Group:

9-day off period. E7272 was administered in the same manner at 40 µg/kg/day.

Intravenous administration

Saline for injection

Rat/Sprague Dawley (CrI:CD(SD))

Main study - 10 animals/sex/group; Recovery study - 5/sex/group were designated for the recovery study from the main study

Age:

8-9 weeks old at initiation of dosing

Observations and Results: changes from control

Parameters	Major findings
Mortality	E7777: There were 2 deaths (males) on Day 25 and Day 38 and 6 moribund euthanasias (3 males and 3 females) between Days 31-39 in the HD group. The animals exhibited decreased activity, increased porphyrin staining, altered fecal consistency, hunched posture and cold to touch. E7272: None.
Clinical Signs	E7777-related clinical observations included those described above and were seen mainly in the HD group. Similar, but less severe clinical signs were observed for the E7272-treated animals.
Body Weights	E7777: In the HD group, ↓ mean body weight was noted in males and females up to 43% and 28%, respectively, compared to the control group. E7272: ↓ mean body weight was noted in males and females up to 16% and 18%, respectively, compared to the control group. In the HD group, ↓ mean food consumption was noted in males and females up to 90% and 50%, respectively, compared to control group between Days 34-37. Treatment of E7272 resulted in ↓ mean food consumption in males and females up to 9% and 26%, respectively, compared to the control group between Days 34-37.
Ophthalmoscopy	Not conducted.
Hematology	E7777: At the HD, the main findings included ↓ lymphocytes (up to 43% in males and 47% in females), and ↑ neutrophils (up to 324% in males and 338% in females), monocytes (up to 283% in males and 354% in females), and basophils (up to 250% in males and females) relative to the control group. ↓ red blood cell parameters were noted including hemoglobin (up to 7% in males and 10% in females), and hematocrit (up to approximately 7% in males and 11% in females). ↑ platelet counts were also noted (up to 42% in males and 38% in females). No E7777-related changes were observed following the recovery period. E7272: Similar, but less severe changes were observed in the E7272-treated group.

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

Clinical Chemistry	E7777: ↑ liver function parameters were noted including aspartate aminotransferase (up to 145% in males and 169% in females) and alanine aminotransferase (up to 206% in males and 171% in females) compared to the control group. These changes were associated with ↓ values of total protein (up to 18% in males and 17% in females), albumin (up to 22% in males and 30% in females), albumin/globulin ratio (up to 11% in males and 39% in females), and cholesterol (up to 45% in males and 54% in females). ↑ renal function parameters were also noted in urea (up to 67% in males and 87% in females) and creatinine (up to 39% in males and 35% in females). E7272: Similar, but less severe changes were observed in the E7272-treated group.
Urinalysis	In the MD and HD groups, transitional cells (grade 1 or 2) were observed in the urinary sediment of males and females (no corresponding histopathologic changes in the urothelium).
Gross Pathology	E7777: Enlargement of lymph nodes and spleen and discoloration of organs including the kidney, liver, Harderian gland, thyroids, gastrointestinal (GI) tract, lungs and adrenal glands were noted. Small size of male reproductive organs were also observed. Most of these changes were noted in the recovery group including the changes in the lymph nodes, spleen, GI tract, lung and thyroid.
Organ Weights	E7777: At the HD, ↓ pituitary weights (up to 48% in males and 28% in females) and ↑ lung (up to 56% in males and 35% in females) and spleen (up to 57% in males and 53% in females) weights were noted relative to the control group. ↓ pituitary weights were observed in the recovery group. E7272: Similar, but less severe changes were observed in the E7272-treated group.
Histopathology	Lymphoid and lymphoid/eosinophilic infiltrations were observed in animals treated with E7272, and organ and tissue distributions were similar to those observed with E7777 at the HD. However, the incidence and severity of the findings were comparable or lower than those observed in the E7777-treated group. There was a partial recovery during the recovery period. Other findings included vacuolation of cortical cells in the adrenal in the E7777- and E7272-treated groups. The secondary changes included regeneration of renal tubular epithelial cells and secondary tubular mineralization in the kidney, kupffer cell hypertrophy and hepatocellular single cell necrosis in the liver, pancreatic atrophy, testicular seminiferous tubule atrophy with decreased spermatozoa in the epididymides, spermatic granuloma in the epididymides with dilatation of the testicular seminiferous tubule, prostatic acinar atrophy and decreased secretion in the seminal vesicles, bone marrow hypocellularity, erosion in the skin and focal/multifocal chronic inflammation in the lung.

Incidence of treatment related lymphoid or lymphoid/eosinophilic infiltration											
Sex		Male					Female				
Organ	Dose (µg/kg)	Cont	TI1 ^a	TI1 ^a	TI1 ^a	TI2 ^b	Cont	TI1 ^a	TI1 ^a	TI1 ^a	TI2 ^b
	No. of animals examined ^c	0	2	10	40	40	0	2	10	40	40
		10	10	10	8	10	10	10	10	9	10
Kidneys		0	2	10	8	9	0	2	7	9	10
Lung		0	0	7	8	9	0	0	1	9	6
Liver		0	0	6	7	8	0	2	5	6	8
Lymph nodes (Submaxillary)		0	0	2	8	9	0	0	3	9	6
Lymph nodes (Mesenteric)		0	0	4	8	5	0	0	1	7	5
Spleen		0	1	8	8	9	0	2	7	8	10
Stomach		0	0	2	7	7	0	0	1	8	7
Trachea		0	0	3	8	4	0	0	2	9	4
Epididymides		0	0	9	8	9	-	-	-	-	-
Prostate		0	3	10	8	6	-	-	-	-	-
Heart		0	0	4	7	6	0	0	2	5	3
Pancreas		0	0	2	8	7	0	0	3	4	4
Salivary Glands		0	0	4	7	2	0	0	4	6	2
Skin		0	0	2	7	4	0	0	2	4	4
Thyroids		0	0	1	6	7	0	0	1	6	4
Coagulating glands		0	0	1	6	4	-	-	-	-	-
Seminal vesicles		0	0	1	5	5	-	-	-	-	-
Eyes		0	1	3	5	2	0	1	2	2	2
Harderian glands		0	1	2	5	4	0	0	4	6	5
Injection site		0	1	2	4	6	0	0	1	6	3
Duodenum		0	0	0	6	1	0	0	0	4	4
Jejunum		0	0	0	4	0	0	0	0	2	1
Ileum		0	0	0	3	0	0	0	0	1	0
Cecum		0	0	1	5	0	0	0	2	4	4
Colon		0	0	0	4	0	0	0	0	1	0
Rectum		0	0	2	3	0	0	2	1	3	3
Tongue		0	0	1	4	2	0	0	0	4	3
Urinary bladder		0	0	0	3	1	0	0	0	1	0
Testes		0	0	4	3	3	-	-	-	-	-
Choroid plexus		0	0	1	0	1	0	0	0	1	1
Esophagus		0	0	0	1	0	0	0	0	0	0
Mammary gland		0	0	0	0	1	0	0	0	0	0
Pituitary		0	0	1	2	2	0	0	0	0	2
Parathyroids		0	0	1	0	0	0	0	0	1	0
Sciatic nerve		0	0	2	2	3	0	0	0	0	0
Skeletal muscle		0	0	0	1	0	0	0	0	1	0
Adrenals		0	0	0	1	0	0	0	0	0	0
Ovaries		-	-	-	-	-	0	0	0	3	0
Uterus		-	-	-	-	-	0	0	0	3	0
Vagina		-	-	-	-	-	0	0	0	1	0

^a, TI1 = Test Item 1; Improved Process E7272
^b, TI2 = Test Item 2; Commercial E7272
^c, Numbers of examined animals were 8 in males and 9 in females in TI1 high dose group due to mortality

(Table excerpted from Applicant's submission)

Toxicokinetics	Refer to section 5.4 ADME/PK. The PK study (Study No. DMPKAP2010-052) was conducted in parallel to this study. The exposure to E7777 was approximately 2-fold that of E7272. Therefore, from a comparative perspective, E7777 may have been overdosed relative to E7272 in this study. Anti-drug antibodies were detected with an inverse dose-response relationship (25/30 rats, 7/30 rats, 2/29 rats and 16/30 rats at 2, 10, and 40 µg/kg E7777, or 40 µg/kg E7272, respectively) after the second cycle of treatment.

LD: low dose; MD: mid dose; HD: high dose

E7777: A 14-Week Intermittent Intravenous Dose Toxicity Study in Rats/B170280

- There were two moribund euthanasias in the HD group. These animals exhibited decreased locomotor activity, loose stool, and decreased body weight and food consumption. The systemic inflammatory response in multiple organs and its effects on the parenchyma was determined to be the cause of moribundity in these animals.
- The main findings included decreased body weight and food consumption and lymphocytic or lymphocytic/eosinophilic infiltration in various organs and tissues.
- The toxicities were observed in the renal tubule, male reproductive organs, and bone marrow (femur and sternum).

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 2, 10, or 20 µg/kg/day for 7 cycles; each cycle consisted of a 5-day on followed by a 9-day off period.
Route of administration:	Intravenous administration
Formulation/Vehicle:	Saline for injection
Species/Strain:	Rat/Sprague Dawley (CrI:CD(SD))
Number/Sex/Group:	Main study - 10/sex/group
Age:	8 weeks old at initiation of dosing
Satellite groups/ unique design:	TK study - 7/sex/group

Observations and Results: changes from control

Parameters	Major findings
Mortality	At the HD, 1 male in the main study (Day 63) and 1 male in the TK study (Day 62) were sacrificed in moribundity. Both animals exhibited decreases in locomotor activity, emaciation, and decreases in body weight (-11% and -35% from the initial body weight) and/or food consumption. The systemic inflammatory response in multiple organs and its effects on the parenchyma was determined to be the cause of moribundity in these animals.
Clinical Signs	In the HD group, E7777-related clinical observations included ear (pinna) swelling in 6/10 males and 2/10 females from Day 18. Whitish discoloration of teeth was noted in 4/10 males and 2/10 females from Day 29. Emaciation was observed in 1/10 male at the end of the experimental period (Day 98). In the MD group, ear swelling was observed in 3/10 males and 4/10 females from Day 18, which disappeared during the study period. Whitish change of teeth was noted in 1/10 female from Day 33 to Day 61.
Body Weights	In the HD group, ↓ mean body weight was noted in males and females up to 18% and 8%, respectively, compared to the control group. In the MD group, ↓ mean body weight was noted in males up to 11% from the control group.
Ophthalmoscopy	Unremarkable.
Hematology	The main findings included ↑ neutrophil, eosinophil, basophil and/or monocyte counts in males on Day 91.

Hematology values in rats									
Test	Study Day	Male				Female			
	µg/kg	0	2	10	20	0	2	10	20
		mean	%Δ	%Δ	%Δ	mean	%Δ	%Δ	%Δ
Basophils (10 ⁹ /L)	35	0.006	0	166.7	666.7	0.005	-60	120	80
	91	0.01	30	0	277.8	0.004	175	-25	100
Eosinophils (10 ⁹ /L)	35	0.17	-1.76	24.12	38.82	0.14	-17.5	37.23	32.12
	91	0.18	6.01	-8.74	179.3	0.14	-10.3	0.74	31.62
	98	0.16	-11.8	-10.56	44.93	0.10	-9	13	-10
Erythrocytes (10 ¹² /L)	35	8.64	0.96	0.46	-2.04	8.42	-0.65	-1.53	-4.04
	91	9.42	-1.06	-0.66	-6.97	8.52	-1.73	-0.88	-3.76
	98	8.14	0.66	0.22	-4.33	7.32	-0.82	-1.63	-1.87
Hematocrit (%)	35	45.6	-0.04	-2.44	-4.78	45.1	-1.13	-4.77	-4.68
	91	47.8	-2.78	-3.22	-9.93	45.5	-3.06	-3.91	-4.95
	98	40.8	-1.08	-2.21	-6.76	38.4	-1.46	-3.02	-1.4
Hemoglobin (g/dL)	35	16.7	0.18	-2.58	-5.29	16.4	-2.5	-4.88	-6.28
	91	17.2	-1.86	-2.26	-9.33	16.4	-3.84	-2.74	-4.81
	98	14.9	-1.14	-1.88	-6.82	14.1	-2.2	-3.05	-2.62
Leukocytes (10 ⁹ /L)	35	12.26	-10.2	-9.93	12.14	8.24	-7.61	17.34	30.03
	91	11.90	-6.73	-4.75	22.3	7.86	-10	-6.78	3.86
	98	9.89	-4.59	3.66	2	5.87	-4.8	23.08	24.74
Monocytes (10 ⁹ /L)	35	0.40	22.89	-11.19	74.13	0.24	11.34	32.35	44.12
	91	0.51	3.9	-11.5	50.96	0.28	-10.4	-11.1	-3.57
	98	0.36	-10.2	0.28	14.48	0.22	1.84	33.64	24.88
Neutrophils (10 ⁹ /L)	35	1.59	-23.1	-16.96	2.07	1.09	-43.8	6.68	11.26
	91	1.72	-10.3	2.51	127.5	1.05	-35.5	5.8	-5.23
	98	2.50	-21.8	-5.09	1.19	1.61	-36.9	-4.4	-32.1
Platelets (10 ⁹ /L)	35	1250	-3.26	1.5	14.89	1236	0.65	5.2	20.22
	91	1210	2.55	5.68	16.61	1243	0.92	-12.1	-7.86
	98	1212	-4.67	0.41	17.71	1205	-2.84	-6.55	-8.57

%Δ= % change from the control values.

Clinical Chemistry	In males, dose-dependent increases in ALT, ALP, and AST were observed compared to the control group. ↑ urea nitrogen was observed in males at the HD. ↓ bilirubin was observed in both males and females at all doses.

Clinical chemistry values in rats at the end of the dosing period (Day 98)								
	Male				Female			
	0	2	10	20	0	2	10	20
$\mu\text{g}/\text{kg}$	mean	% Δ	% Δ	% Δ	mean	% Δ	% Δ	% Δ
Alanine Aminotransferase (ALT; U/L)	26	11.15	15	71.37	31	41.61	86.45	-17.74
Alkaline Phosphatase (ALP; U/L)	213	1.55	7.73	19.91	116	12.09	7.43	-3.45
Aspartate Aminotransferase (AST; U/L)	79	4.46	9.55	41.83	99	1.51	31.79	-13.78
Bilirubin (mg/dL)	0.1	-20	-10	-11.1	0.1	-16.67	-8.33	-16.67
Potassium (mmol/L)	4.3	-0.94	1.64	4.09	4.1	4.36	5.33	6.78
Urea Nitrogen (mg/dL)	12.9	0	9.07	58.48	15.3	-1.57	2.22	3.26

% Δ = % change from the control values.

Urinalysis	In the MD and HD groups, transitional cells (grade 1 or 2) were observed in the urinary sediment of males and females (no corresponding histopathologic changes in the urothelium).
Gross Pathology	Swelling of the pinna was observed at $\geq 10 \mu\text{g}/\text{kg}$ in both sexes. In males, small thymus, testis, epididymis, prostate, and seminal vesicle, whitish patch on the liver, pale discoloration of the kidney, and enlargement of the thyroid gland were observed at the HD.
Organ Weights	$\downarrow$ testis weight was noted in males at the HD (absolute weight: -27%; organ to body weight ratio: -6%).
Histopathology	E7777-related microscopic changes of lymphocytic or lymphocytic/eosinophilic infiltration in multiple organs and tissues were noted. These organs included the tongue, stomach, duodenum, kidney, and pinna in both sexes. The infiltration in the heart, aorta, mandibular and mesenteric lymph nodes, trachea, lungs, jejunum, ileum, liver, pancreas, submandibular and sublingual salivary glands, incisor, molar, testis, epididymis, prostate, seminal vesicle, coagulation gland, thyroid gland, brain, Harderian gland, femoral muscle and skin was only noted in males.

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

Selected microscopic parameters at the end of the dosing period										
Organ/Tissue	Finding	Severity	Male				Female			
		µg/kg	0	2	10	20	0	2	10	20
EPIDIDYMIS		# Animals	10	10	10	10	0	0	0	0
	Atrophy, Duct, Bilateral; Unilateral	1 OF 5				3	N/A	N/A	N/A	N/A
		2 OF 5				2	N/A	N/A	N/A	N/A
	mineralization, Mononuclear cell	1 OF 5		1	3	1	N/A	N/A	N/A	N/A
	Infiltrate, Lymphocyte/eosinophil	2 OF 5				3*	N/A	N/A	N/A	N/A
	Single cell necrosis, Epithelial cell	1 OF 5				1	N/A	N/A	N/A	N/A
2 OF 5					2	N/A	N/A	N/A	N/A	
TESTIS		# Animals	10	10	10	10	0	0	0	0
	Atrophy, Seminiferous epithelium	2 OF 5			1	1	N/A	N/A	N/A	N/A
		3 OF 5				4	N/A	N/A	N/A	N/A
	Infiltrate	1 OF 5				2	N/A	N/A	N/A	N/A
2 OF 5					4	N/A	N/A	N/A	N/A	
PINNA		# Animals	10	10	10	10	10	10	10	10
	Auricular chondropathy	1 OF 5			2	3*			1	
		2 OF 5			2	3			1	2
		3 OF 5				1			2	
	Infiltrate	1 OF 5	1			2				2
		2 OF 5				1				
3 OF 5					1					
KIDNEY		# Animals	10	10	10	10	10	10	10	10
	Infiltrate, lymphocyte	2 OF 5				2*				1
		3 OF 5				1				
	Regeneration, tubule	2 OF 5				2*				
3 OF 5					1					
GLAND, PROSTATE		# Animals	10	10	10	10	0	0	0	0
	Atrophy, Acinus	1 OF 5				2	N/A	N/A	N/A	N/A
		2 OF 5				1*	N/A	N/A	N/A	N/A
	Infiltrate, lymphocyte	2 OF 5				3	N/A	N/A	N/A	N/A
3 OF 5					1*	N/A	N/A	N/A	N/A	
GLAND, COAGULATING		# Animals	10	10	10	10	0	0	0	0
	Decrease, Secretory substance	1 OF 5				1				
		2 OF 5				2				
	Infiltrate, lymphocytes	1 OF 5				1				
2 OF 5					2					
GLAND, SEMINAL VESICLE		# Animals	10	10	10	10	0	0	0	0
	Decrease, Secretory substance	2 OF 5				1	N/A	N/A	N/A	N/A
		3 OF 5				2*	N/A	N/A	N/A	N/A

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

	Infiltrate, lymphocyte	2 OF 5				3*	N/A	N/A	N/A	N/A
TOOTH, INCISOR		# Animals	10	10	10	10	10	0	0	10
	Atrophy, Papillary layer	1 OF 5				3*				
	Infiltrate, lymphocyte; Periodontal tissue	1 OF 5				1				
		2 OF 5				2*				
TOOTH, MOLAR		# Animals	10	10	10	10	10	0	0	10
	Infiltrate, lymphocyte; Gingiva	1 OF 5		1	3	4				
		2 OF 5				2				
GLAND, ADRENAL		# Animals	10	10	10	10	10	0	0	10
	Vacuolation, cortical cell, fascicular zone	1 OF 5				2				
		2 OF 5				1*				
HEART		# Animals	10	10	10	10	10	0	0	10
	Infiltrate, lymphocyte	2 OF 5				1				
		3 OF 5				1*				
LUNG/BRONCHUS		# Animals	10	10	10	10	10	0	0	10
	Infiltrate, Lymphocyte/ eosinophil	2 OF 5				2*				
PANCREAS		# Animals	10	10	10	10	10	0	0	10
	Infiltrate	2 OF 5				3*				
SMALL INTESTINE, ILEUM		# Animals	10	10	10	10	10	0	0	10
	Infiltrate, Lymphocyte/ eosinophil; Macrophage; Peyers patch	1 OF 5				3				
STOMACH		# Animals	10	10	10	10	10	10	10	10
	Infiltrate, Lymphocyte/ eosinophil	2 OF 5				1*				1
		3 OF 5				2				
BONE MARROW, FEMUR		# Animals	10	10	10	10	10	0	0	10
	Increase, Hematopoietic cell, Granulocytic	2 OF 5				2*				
		3 OF 5				1				
BONE MARROW, STERNUM		# Animals	10	10	10	10	10	0	0	10
	Increase, Hematopoietic cell, Granulocytic	1 OF 5				2*				
		2 OF 5				1				
GLAND, THYROID		# Animals	10	10	10	10	10	0	0	10
	Inflammation, Lymphocytic	2 OF 5			1	1*				
		3 OF 5				1				
		4 OF 5				1				
		# Animals	10	10	10	10	10	0	0	10

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

LYMPH NODE, MESENTERIC	Infiltrate, Lymphocyte/ eosinophil	1 OF 5				2				
		2 OF 5				1				
SMALL INTESTINE, DUODENUM	Infiltrate, Lymphocyte/ eosinophil	# Animals	10	10	10	10	10	10	10	10
		1 OF 5								1
SMALL INTESTINE, JEJUNUM	Infiltrate, Lymphocyte/ eosinophil	2 OF 5				3*				
		# Animals	10	10	10	10	10	0	0	10
THYMUS	Atrophy	1 OF 5				1				
		2 OF 5				1				
ARTERY, AORTA	Infiltrate, Lymphocyte/ eosinophil	3 OF 5				1*				
		# Animals	10	10	10	10	10	0	0	10
BRAIN	Infiltrate	1 OF 5				2*				
		# Animals Examined	10	10	10	10	10	0	0	10
GLAND, HARDERIAN	Infiltrate, lymphocyte	2 OF 5				1				
		3 OF 5				1				
GLAND, PITUITARY	Hypertrophy, Basophil, Pars distalis	# Animals	10	10	10	10	10	0	0	10
		3 OF 5				2				
GLAND, SALIVARY, SUBLINGUAL	Infiltrate, lymphocyte	1 OF 5				1				
		2 OF 5				1*				
GLAND, SALIVARY, SUBMANDIBULAR	Infiltrate, lymphocyte	3 OF 5				2*				
		# Animals	10	10	10	10	10	0	0	10
LARGE INTESTINE, CECUM	Infiltrate, Lymphocyte/ eosinophil	1 OF 5				2*				
		# Animals	10	10	10	10	10	0	0	10
LARGE INTESTINE, COLON	Infiltrate, Lymphocyte/ eosinophil	1 OF 5				2				
		# Animals	10	10	10	10	10	0	0	10
LIVER	Infiltrate, Lymphocyte/ eosinophil	2 OF 5				2				
		# Animals	10	10	10	10	10	0	0	10
SKIN	Infiltrate, Lymphocyte/ eosinophil	2 OF 5				1*				
		3 OF 5				1				

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

TONGUE		# Animals	10	10	10	10	10	10	10	10
	Infiltrate, lymphocyte	2 OF 5				2*				1
TRACHEA		# Animals	10	10	10	10	10	0	0	10
	Infiltrate	2 OF 5				2*				

Blank cells: not toxicologically significant, 1= minimal, 2= mild, 3= moderate, 4= marked, 5= severe, * Finding was in both animal(s) with early mortality and surviving animals.

Toxicokinetics

The exposure (C_{max} and AUC_{0-5h}) increased with dose on Day 1. At the MD and HD, the exposures of E7777 decreased on Day 29 and were below the limit of quantification (BLQ) on Day 85, which is likely due to anti-E7777 antibodies. No sex differences were observed in exposure at any of the dose levels. The findings are summarized in the table below.

Anti-E7777 antibodies were detected from Day 28 in all dose groups. At the LD, 71% of males and 57% of females showed anti-E7777 antibodies. At the MD and HD, most animals showed anti-E7777 antibodies from Day 28.

Summary of E7777 Toxicokinetic Parameters in Rat Plasma (14 Week)

Dose ($\mu\text{g}/\text{kg}$)	Day	Male		Female	
		C_0 (ng/mL)	AUC_{0-5h} (ng·h/mL)	C_0 (ng/mL)	AUC_{0-5h} (ng·h/mL)
2	1	34.3 ± 7.9	14.1 ± 2.6	34.5 ± 10.4	13.3 ± 3.9
	29	41.1 ± 6.5	21.7 ± 7.6	37.7 ± 12.8	14.4 ± 4.8
	85	47.4 ± 11.4	27.9 ± 13.1	52.8 ± 10.8	22.9 ± 8.8
10	1	224 ± 16	161 ± 22	286 ± 47	164 ± 14
	29	158 ± 83	84.9 ± 61.3	159 ± 115	66.3 ± 55.3
	85	N.C.	N.C.	N.C.	N.C.
20	1	551 ± 44	392 ± 57	579 ± 37	310 ± 58
	29	202 ± 208	57.4 ± 87.9	218 ± 214	94.7 ± 162.9
	85	N.C.	N.C.	N.C.	N.C.

Data represent the mean ± SD of 7 animals. N.C.: Not calculated
(Excerpted from Applicant's submission)

LD: low dose; MD: mid dose; HD: high dose

5.5.2. **Genetic Toxicology**

The Applicant's Position:

DD (as E7272) was not genotoxic in vitro in the Ames test (bacterial culture) and the chromosomal aberration test (Chinese hamster ovary cells) as reported in BLA 103767.

The FDA's Assessment:

The FDA concurs with the Applicant.

5.5.3. **Carcinogenicity**

The Applicant's Position:

No carcinogenicity studies for E7272 or E7777 were conducted, in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S6 and S9 guidelines.

The FDA's Assessment:

The FDA concurs with the Applicant.

5.5.4. **Reproductive and Developmental Toxicology**

The Applicant's Position:

Embryofetal toxicity studies have not been conducted for E7777 or E7272.

DD is capable of selectively and dose-dependently killing high-affinity IL-2 receptor-expressing Tregs, which are important for protecting the fetus from a maternal immune response. The Applicant therefore believes that significant risks to pregnancy have already been established based on the immune system-mediated hazard identified in the literature and that an embryofetal toxicity study with E7777 is not necessary to further define potential risks. A scientific justification as outlined in ICH S9 Guidance on anticancer pharmaceuticals is included in the Nonclinical Overview (Section 2.4) of this BLA.

Other studies including fertility, or effects on pre- and postnatal development were also not conducted with E7777 or E7272 consistent with the recommendations in the ICH S9 guideline.

The FDA's Assessment:

To address the potential effects of DD on embryo-fetal development, the Applicant submitted an assessment of the reproductive and developmental risk using a weight-of-evidence (WoE) approach. The relevant information is summarized below and indicates that the main reproductive risk for DD is Treg ablation during pregnancy.

The WoE risk assessment includes the following information; references cited were provided by the Applicant:

Tregs are important for immune tolerance during pregnancy by protecting the fetus from a maternal immune response and ensure a robust placenta and sustainable pregnancy. Based on its mechanism of action and pharmacodynamic effects observed in animals and humans, DD causes Treg depletion and this may lead to reproductive disorders.

1. In murine models, Tregs have been shown to play an essential role in placental development and maintenance of pregnancy by suppressing inflammation and preventing adverse effects of anti-fetal alloantigen T effector cells (Aluvihare, et al., 2004; Zenclussen, et al., 2005).
2. Normal pregnancy in humans and mice is characterized by an increased number of Tregs as compared to non-pregnant individuals. Insufficient Treg numbers or inadequate functional competence are implicated in infertility, recurrent miscarriage, and placental insufficiency causing preeclampsia, fetal growth restriction, and excessive inflammation in the uterus and gestational tissues (Zenclussen, 2006; Jasper, et al., 2006; Li, et al., 2017; Robertson, et al., 2018).
3. Women with unexplained infertility exhibit lower expression of the Treg cell marker FOXP3 mRNA in endometrial tissue. Additionally, Tregs are emerging as important regulators of the maternal vascular changes that are essential for normal placental development and adequate placental access to maternal blood (Jasper, et al., 2006).

5.5.5. Other Toxicology Studies

The Applicant's Position:

E7272 and E7777 are protein products, and no phototoxicity studies were conducted, consistent with the recommendations in the ICH S10 guideline. An assessment of phototoxic potential is included in the Nonclinical Overview (2.4) of this BLA.

DD contains (b) (4) variants, (b) (4), and the toxicity and PK of these variants was evaluated in rats. There were no differences in PK, and the toxicologic profile was the same for both variants, however, (b) (4) was slightly less toxic, and (b) (4) slightly more toxic than E7272. The differences in toxicity between E7272 and the (b) (4) variants are likely to be clinically insignificant. A study on toxicity of E7272 compared with two molecules with amino acid changes in either the diphtheria toxin (DT) portion of the molecule or in the IL-2 portion of the molecule confirmed that both the enzymatic and IL-2 receptor binding domains must be intact in order to induce pharmacology and toxicity associated with the fully functional molecule.

The FDA's Assessment:

The FDA concurs with the Applicant.

Impurity Qualification

CMC consulted Pharmacology/Toxicology and asked if the limit of quantification (LOQ) established for the impurity (b) (4) at (b) (4) ng/mL is acceptable. The level of (b) (4) in the drug substance is <LOQ and the level at LOQ provides a sufficient safety margin compared to

the acceptable daily intake (ADI) based on data from animal studies. The CMC team also asked if the (b) (4) level observed in the leachable study is acceptable. Based on ICH Q3C Impurities: Residual Solvents, (b) (4) is classified as a Class 3 residual solvent with a permitted daily exposure (PDE) of (b) (4) mg/day. Pharmacology/Toxicology has no concerns with the LOQ level of (b) (4) or the level of (b) (4).

X

X

Primary Reviewer

Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

Denileukin diftitox (E7777) is a recombinant cytotoxic fusion protein consisting of the amino acid sequences for diphtheria toxin (DT) fragments A and B and for human interleukin-2. After endocytosis, the DT fragment is cleaved and blocks ribosomal translation, resulting in cellular death. The proposed dosing regimen is 9 µg/kg/day by intravenous (IV) infusion over 60 minutes for 5 consecutive days every 21 days, repeated for as long as the patient receives clinical benefit.

E7777 has the same active monomer as ONTAK (BLA 103767; initial U.S. approval in February 1999) but has higher purity. The recommended doses for ONTAK are 9 or 18 µg/kg/day by IV infusion over 30 to 60 minutes for 5 consecutive days every 21 days for 8 cycles. (b) (4)

The clinical pharmacology package includes data from three clinical studies, pharmacometrics analyses, and an evaluation of immunogenicity. The pivotal trial is E7777-G000-302 (Study 302), a completed, multicenter, open-label, single-arm, Phase 3 study in subjects with recurrent or persistent CD25-positive cutaneous T-cell lymphoma (CTCL). Two studies completed in Japan (Study E7777-J081-101 [Study 101] and Study E7777-J081-205 [Study 205]) in patients with either CTCL or peripheral T cell lymphoma (PTCL) provide supportive evidence. The Applicant's pharmacometrics analyses include population PK analyses and exposure-response analyses for safety using pooled data from the three studies, as well as exposure-response analyses for efficacy using data from Study 302.

The clinical pharmacology review focused on 1) the acceptability of the proposed dosing regimen; 2) the effects of anti-drug antibodies (ADAs) on pharmacokinetics (PK), safety, and efficacy of E7777; and 3) the impact of CD25 expression on the efficacy of E7777 in addition to its appropriateness as a biomarker of interest (b) (4).

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761312. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations are summarized below in Table 3.

Table 3: Key Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness is the overall response rate (ORR) observed in Study 302 (see Section 8.1). Sixty-nine patients with recurrent or persistent stage I-III CD25-positive CTCL were treated at the proposed recommended dosing regimen. Data from Study 101, Study 205, and the exploratory exposure-response analyses for efficacy provided supportive evidence for effectiveness.
General dosing instructions	The proposed recommended dosing regimen (9 µg/kg/day by IV infusion over 60 minutes for 5 consecutive days every 21 days) is acceptable for approval in the general patient population. - The recommended dosing regimen demonstrated clinically meaningful ORR and an acceptable safety profile in patients treated at the proposed recommended dose in Study 302. - Clinical data collected at alternative dosing regimens are limited. Exploratory exposure-response analyses do not suggest that an alternative dosing regimen would improve the risk/benefit profile.
Dosing in patient subgroups	- No therapeutic individualization of E7777 is needed based on age, sex, race, mild or moderate renal impairment (creatinine clearance [CLcr] 30-89 mL/min, estimated per the Cockcroft–Gault formula), or mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN, or total bilirubin 1 to 1.5 times ULN and any AST). Limited data are available in patients with severe renal impairment (creatinine clearance 15 to 29 mL/min, n=2). The effect of moderate (total bilirubin >1.5 to 3 times ULN and any AST) or severe hepatic impact (total bilirubin >3 times ULN and any AST) on E7777 PK is unknown. - No dose adjustment is needed based on the presence of ADAs. While the formation of ADAs is associated with a decrease in measured E7777

Review Issue	Recommendations and Comments
	serum concentration, available data does not suggest an adverse impact on safety or efficacy. 3. No dose adjustment is needed based on CD25 expression level. (b) (4)
Drug-drug interactions	No clinical drug interaction studies were conducted with E7777. Dedicated studies are not required given that E7777 is not expected to have drug-drug interaction potential with major CYP enzymes or transporters.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Mechanism of Action

E7777 is a recombinant cytotoxic fusion protein consisting of DT fragments A and B (amino acid sequence of (Met₁-Thr₃₈₇)-His) and human interleukin-2 (IL-2; amino acid sequence of Ala₁-Thr₁₃₃). E7777 is designed to direct the cytotoxic action of DT to cells that express the IL-2 receptor and to deplete Tregs which are recruited into tumor infiltrates to assist tumors in evading host immune surveillance.

Pharmacokinetics

After the first dose, E7777 displayed 2-compartment behavior with a distribution phase (half-life approximately 1.4 minutes) and a terminal phase (half-life approximately 68 minutes). Mean clearance was approximately 0.59 mL/minute/kg and the median steady-state volume of distribution was 0.046 L/kg, assuming a 75 kg individual. Mean clearance increased approximately 6-fold from Cycle 1 to Cycle 3 corresponding to a decrease in exposure of approximately 78%. No accumulation was evident between the first and fifth doses.

Immunogenicity

Immunogenicity of E7777 was evaluated using two electrochemiluminescence-based (ECL) immunoassays for the detection of antibodies (Abs) against E7777 and against the IL-2 domain and two cell-based assays for detection of neutralizing antibodies (NABs).

In Study 302, among patients with any stage CTCL who received E7777 9mcg/kg/day:

- Prior to treatment with E7777, 78.0% (71/91) of subjects had anti-E7777 Abs (presumably due to widespread diphtheria vaccination) and 7.7% (7/91) of subjects had anti-E7777 NABs; 5.5% (5/91) had anti-IL-2 Abs but none had anti-IL-2 NABs.
- After treatment with E7777, 92.9% (78/84) and 82.1% (69/84) of subjects had anti-E7777 Abs and IL-2 Abs, respectively; 11.6% (8/69) of subjects had anti-IL-2 NABs.

- Treatment with E7777 led to an increase in Ab titers. The median anti-E7777 Ab titers were 151, 181, 84, and 59 times higher than baseline at Day 1 of Cycle 2, Cycle 3, Cycle 5, and Cycle 8, respectively. The anti-IL-2 Ab titers were 2, 49, 437, and 1312 times higher than baseline at these same visits, respectively.

Anti-Drug Antibody Effects on Pharmacokinetics

The presence of pre-existing anti-E7777 Abs in the first dosing cycle could form drug/antibody complexes and prevent the ability of the method to quantify E7777 in some subjects while drug may be available in the circulation. In a subset of subjects in Study 302 (N=12), treatment-emergent anti-E7777 and/or anti-IL-2 Abs reduced E7777 maximum observed concentration (C_{max}) and AUC from zero to time $t_{(0-t)}$ to 60 to 67% and 84 to 87%, respectively, in Cycle 3 and 5 compared with those of Cycle 1 and is in line with changes in exposure estimated using a population approach.

Anti-Drug Antibody Effects on Efficacy

During the treatment cycles with E7777 in Study 302, objective response rate (ORR) was 32.1% (25/78) in anti-E7777 Ab-positive subjects and 36.2% (25/69) in anti-IL-2 Ab-positive subjects.

Anti-Drug Antibody Effects on Safety

The observed incidence of treatment-emergent adverse events (TEAEs) was generally lower in anti-E7777 or anti-IL-2 Abs-positive subjects. The incidence of capillary leak syndrome (CLS) in Study 302 was lower in anti-E7777 Abs-positive subjects (21.8% [17/78]) and anti-IL-2 Abs-positive subjects (19.1% [13/68]) than in anti-E7777 Ab-negative subjects (83.3% [5/6]) and anti-IL-2 Ab-negative subjects (60.0% [9/15]). The presence of either anti-E7777 or anti-IL-2 Abs did not adversely impact the safety profile of E7777.

The Applicant's Position:

The PK profile of E7777 was appropriately evaluated and is similar to Ontak. Renal and hepatic impairment studies have not been conducted. There were no clinically significant differences in PK in neither mild-moderate renal impairment ($CrCL >24$ mL/min) nor by albumin level (24-49 g/L). Food-drug and drug-drug interactions are not expected. Immunogenicity profiles of E7777 were appropriately evaluated in the E7777 clinical studies.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of the clinical pharmacology properties of E7777. However, (b) (4) titer cut-point may slightly affect final reporting of immunogenicity results without affecting any final conclusions. Therefore, this update to reporting may be deferred to the next review cycle. General clinical pharmacology and PK characteristics of E7777 based on FDA review is summarized in Section 6.3.1.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data and The Applicant's Position:

Selection of dose for the Main Study in Study 302 was based on a Lead-in part, in which a continual reassessment method was used to establish the maximum tolerated dose (MTD) of E7777, targeting a dose-limiting toxicity (DLT) rate of approximately 20%. The MTD was 12 µg/kg. The dose of E7777 selected for the Main Study was 9 µg/kg, as recommended by the Protocol Steering Committee, based on the totality of safety and efficacy data. The 15 µg/kg dose of E7777 was judged not to be tolerable (2/2 DLTs, both CLS); no subjects treated at 9 µg/kg (0/8) discontinued treatment due to AEs, whereas 3/9 subjects in the 12 µg/kg group discontinued treatment due to AEs. Regarding efficacy, there were 4/8 responses at 9 µg/kg and 2/7 responses at 12 µg/kg in the efficacy evaluable population; thus it did not appear that efficacy would be compromised by selecting the lower dose of 9 µg/kg. Data from the Phase I Study 101 were also taken into consideration; in that study, the MTD and the recommended dose of E7777 was 9 µg/kg.

The FDA's Assessment:

The clinical pharmacology review team agrees that the proposed recommended dose of 9 µg/kg E7777 is acceptable for the general population of adult patients with relapsed or refractory stage I-III CTCL. The 9 µg/kg dose selected based on data from the Study 302 Lead-In part was further evaluated in the Study 302 Main Study and demonstrated clinically meaningful ORR and an acceptable safety profile. In addition, available data do not support an alternative dosing regimen that would significantly improve the risk/benefit profile. Refer to Section 6.3 for data and analyses supporting the proposed dosing regimen.

6.2.2.2. Therapeutic Individualization

Data:

Data from Study 302, Study 205, and Study 101 were used to derive conclusions related to E7777 PK and the exposure-response of E7777. No clinically significant differences in the PK of E7777 were observed based on age (23 to 86 years), sex, race, body weight (39 to 148 kg), Eastern Cooperative Oncology Group (ECOG) performance status (0 to 2), serum albumin (24-49 g/L), or mild to moderate renal impairment (creatinine clearance >24 mL/min). Hepatic and renal impairment studies with E7777 have not been conducted.

A subject-level E7777 exposure-safety analysis of adverse events of special interest (AESI), which included CLS, hepatotoxicity, visual impairment, infusion reaction, hypersensitivity, infection, thrombotic events, and rash, was conducted. The analysis included data from all subjects with CTCL, PTCL or other lymphomas across E7777 studies, who received E7777 at any

dose level (6, 9, 12, or 15 µg/kg). Multivariate logistic regression analysis for each AESI of any CTCAE grade was performed for all AESIs except for ‘thrombotic events’ due to the very low incidence (2.5%) of this event.

The objective of this analysis was to describe the impact of E7777 exposure and anti-drug antibody information in the presence of covariates. The models included a set of prespecified predictor variables at baseline: age, body weight, sex, race, disease history, ECOG performance status, albumin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, bilirubin and serum creatinine. Subsequently, this logistic regression analysis examined the impact of both anti-E7777 and anti-IL-2 anti-drug antibodies and E7777 drug exposure across the models, considering average daily concentration (C_{av}).

Exposures on Cycle 1 Day 5 for CLS and Cycle 1 Day 1 for hepatotoxicity were positively associated with the AESI, as statistically significant predictors of the models. Log odds of CLS were associated with a 7% increase for a unit of E7777 exposure (C_{av}). The log-transformed E7777 concentrations on Cycle 1 Day 1 were associated with an increased probability of hepatotoxicity, odds ratio (OR) estimate 2.9. Hepatotoxicity TEAEs were transient rises in transaminases that peaked in Cycle 1, declined in Cycle 2, and returned to baseline in Cycle 3. There were no confirmed cases of drug-induced liver injury or cases meeting the criteria for Hy’s law. Conversely, the incidence of infusion reactions was negatively associated with E7777 concentrations under the proposed models (OR=0.37). For other endpoints, the E7777 exposure OR was close to 1 with the 95% confidence interval including 1. Little, if any, positive association with AESI incidence is noted with estimates of anti-E7777 or anti-L-2 antibody titers across the AESI endpoints. Anti-IL-2 antibody titers were positively associated with only the low frequency AESI ‘rash’ (OR=1.32), with a statistically significant parameter ($p<0.05$).

The Applicant’s Position:

All models should be interpreted with caution given the small sample size, heterogeneity of the pooled studies, and the high extent of dropout of subjects across studies, which confounds interpretation of estimated covariate effect size. Given the absence of a clinically meaningful impact of E7777 PK covariate effects in the exposure-safety response and immunogenicity impact analyses, therapeutic individualization by adjustment of the starting dose of E7777 (9 µg/kg) is not deemed warranted.

The FDA’s Assessment:

The clinical pharmacology review team agrees that therapeutic individualization is not required based on intrinsic factors including age (23 to 86 years), sex, race (51% White, 12% African American/Black, 32% Asian), ECOG status (0 to 2), mild to moderate renal impairment (CLCr >30 mL/min), or mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN, or total bilirubin 1 to 1.5 times ULN and any AST). There was limited data in patients with severe renal impairment (CLCr 15 – 29 mL/min, n=2) but their AUC and clearance values were consistent with patients

without renal impairment. No patients with moderate or severe hepatic impairment were studied. Dedicated PK studies in patients with moderate or severe hepatic impairment are not required given that E7777 is not expected to be substantially eliminated via the renal and hepatic pathways. Additionally, dose adjustment based on pre-existing ADA or CD25 expression is not required. Refer to section 6.3 and 19.4 for additional details.

6.2.2.3. Outstanding Issues

Data and The Applicant's Position:

The Applicant believes there are no outstanding issues.

The FDA's Assessment:

The review team agrees that there are no outstanding clinical pharmacology issues.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Following the first dose, E7777 displayed 2-compartment behavior with a distribution phase (half-life approximately 1.4 minutes) and a terminal phase (half-life approximately 68 minutes). Median clearance was approximately 0.59 mL/min/kg and the median steady-state volume of distribution was 0.046 L/kg, assuming a 75 kg individual. The mean clearance increased approximately 6-fold from Cycle 1 to 3 corresponding to a decrease in exposure of approximately 78 %. No accumulation was evident between the first and fifth doses. [REDACTED] and age are not associated with an effect on PK of E7777.

E7777 is a recombinant fusion protein metabolized by proteases into peptides with likely little to no residual biological activity. No drug interaction studies with E7777 have been conducted. No clinically significant differences in the PK of E7777 were observed based on age, sex, race, body weight, ECOG performance status, albumin, or mild to moderate renal impairment. Hepatic and renal impairment studies with E7777 have not been conducted.

The Applicant's Position:

The clinical pharmacology profile of E7777 is consistent with the profile of DD (ONTAK).

The FDA's Assessment:

General clinical pharmacology and PK characteristics of E7777 based on FDA review is summarized below.

General Information

Bioanalysis	Serum E7777 was measured by electrochemiluminescence [ECL]-based ligand binding assays in Studies 101, 205, and 302.																				
Dose Proportionality	While measured exposure of E7777 increased with dose, limited amounts of data at doses other than 9 µg/kg/day preclude a conclusion on dose proportionality in E7777 exposure.																				
Accumulation	There was no accumulation observed between the first and fifth doses.																				
Drug Exposure	The geometric mean (CV%) PK parameters in the 20 patients who received the recommended dose in Study 302 are summarized below. <table border="1"> <thead> <tr> <th></th> <th colspan="3">9 µg/kg E7777 (Study 302)</th> </tr> <tr> <th>Cycle</th> <th>C1D1 (n=20)</th> <th>C3D1 (n=16)</th> <th>C5D1 (n=12)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng/mL)</td> <td>94.4 (76.8%)</td> <td>41.1 (101%)</td> <td>29.9 (120%)</td> </tr> <tr> <td>AUC_{0-t} (min*ng/mL)</td> <td>10340 (168%)</td> <td>2322 (107%)</td> <td>1619 (160%)</td> </tr> <tr> <td>AUC_{0-inf} (min*ng/mL)</td> <td>20743 (59.8%)</td> <td>NC</td> <td>4630 (NE)</td> </tr> </tbody> </table>		9 µg/kg E7777 (Study 302)			Cycle	C1D1 (n=20)	C3D1 (n=16)	C5D1 (n=12)	C _{max} (ng/mL)	94.4 (76.8%)	41.1 (101%)	29.9 (120%)	AUC _{0-t} (min*ng/mL)	10340 (168%)	2322 (107%)	1619 (160%)	AUC _{0-inf} (min*ng/mL)	20743 (59.8%)	NC	4630 (NE)
	9 µg/kg E7777 (Study 302)																				
Cycle	C1D1 (n=20)	C3D1 (n=16)	C5D1 (n=12)																		
C _{max} (ng/mL)	94.4 (76.8%)	41.1 (101%)	29.9 (120%)																		
AUC _{0-t} (min*ng/mL)	10340 (168%)	2322 (107%)	1619 (160%)																		
AUC _{0-inf} (min*ng/mL)	20743 (59.8%)	NC	4630 (NE)																		
Population PK Model	E7777 PK was described by a 2-compartment model and time-dependent clearance to account for the decrease in serum E7777 concentration upon repeated administration. Refer to section 19.4 for details.																				
<i>Distribution</i>																					
Volume of Distribution	The geometric mean (CV%) volume of distribution is 5.0 L (42.6%) after the first dose in 20 patients who received the recommended dose and intensive PK sampling in Study 302.																				
<i>Elimination</i>																					
Half-Life and Clearance	The geometric mean (CV%) clearance is 36.5 mL/min (72.9%) after the first dose in 20 patients who received the recommended dose and intensive PK sampling in Study 302. The mean (CV%) terminal half-life is 112 minutes (30.7%).																				
<i>Specific Populations</i>																					
Intrinsic Factors	The volume of distribution and clearance of denileukin diftitox-cxd1 increase with increasing body weight (39 kg to 148 kg). No clinically significant differences in the pharmacokinetics of E7777 were observed based on age (23 to 86 years), sex, race (51% White, 12% African American/Black, 32% Asian), ECOG status (0 to 2), creatinine clearance (≥24 mL/min), or mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN, or total bilirubin 1 to 1.5 times ULN and any AST).																				

	There is limited data in patients with severe renal impairment (n=2; 15 mL/min $\leq$ CLcr < 30 mL/min). However, the predicted clearance and AUC values in these two patients were comparable to those in patients with normal renal function. The effect of renal impairment on PK exposure was not reported for ONTAK. No data is available in patients with moderate or severe hepatic impairment. However, dedicated PK studies in patients with severe renal impairment and moderate or severe hepatic impairment are not required because E7777 is not expected to be eliminated via hepatic clearance.
Other	
Immunogenicity	In patients who received the recommended dose in Study 302, 78% (71/91) and 5.5% (5/91) had pre-existing antibodies against E7777 and IL-2, respectively. Almost eight percent (7.8%; 7/91) of the subjects had neutralizing anti-E7777 antibodies, but none had neutralizing antibodies against IL-2. On Cycle 3 Day 1, 97% (68/70) and 93% (65/70) of patients evaluable for immunogenicity were positive for ADAs against E7777 and IL-2, respectively; 87% (52/60) and 13% (8/60) were positive for neutralizing antibodies against E7777 and IL2, respectively. Available data does not suggest an adverse impact by anti-drug antibodies on the safety and efficacy of E7777.
Drug Interactions	No clinical drug interaction studies were conducted with E7777, and no clinically relevant drug-drug interactions are anticipated.
CD25 Expression Level	The measurement of CD25 expression is variable within patients. (b) (4) Refer to Section 6.3.3 for details.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data and The Applicant's Position:

Exposure-response relationships for efficacy endpoints were assessed using IRC or investigator best overall response (BOR) based on GRS per Olsen, et al., 2011, BOR in skin based on mSWAT score per Olsen, et al., 2011, and maximum percentage reduction in skin tumor burden (mSWAT score) from baseline for the Primary Efficacy Analysis Set for Study 302. The relationship of BOR relative to E7777 exposure was explored across treatment cycles and

treatment days using graphical analyses. At the 9 µg/kg dose, complete responders exhibited consistently higher E7777 exposures (C_{max} and AUC(0-inf)) over partial and stable responders and individuals classified with progressive disease. This is evident over the initial, Cycle 1, 5-day treatment, for the PK/PD Primary Efficacy Analysis Dataset and PK/PD Full Efficacy Analysis Dataset. The exposure-response relationship was less apparent as the number of subjects and exposures decreased over subsequent treatment cycles.

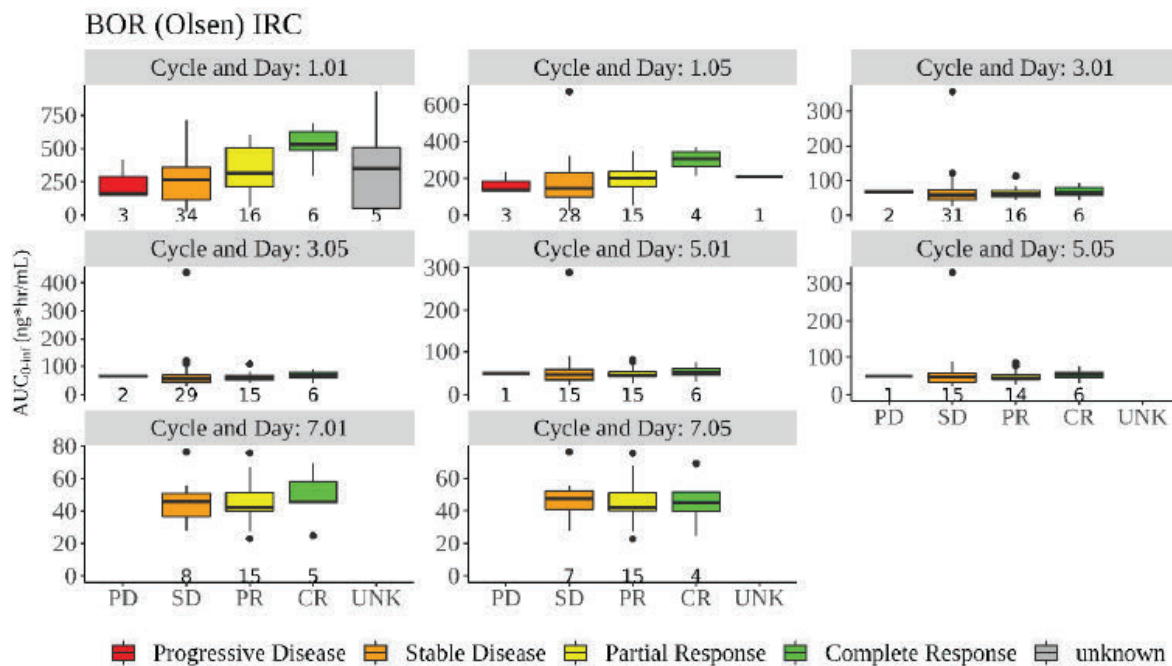
These graphical analyses of efficacy exposure-response provided supportive evidence of effectiveness of E7777 and suggest similar effectiveness to ONTAK.

The FDA's Assessment:

The review team agrees that the clinical pharmacology program provides supportive evidence of effectiveness. Even though the small sample size and narrow dose range in the primary efficacy dataset precludes definitive conclusions on the exposure-response relationship for efficacy endpoints, exploratory analyses results suggest a trend for positive association between early exposure of E7777 and best observed response (BOR) or ORR.

- The Applicant's preliminary E-R analysis by graphical exam suggested a trend for a positive association between early exposure of E7777 and BOR per Olsen criteria assessed by IRC (Figure 1) in 64 patients with Stage I-III CTCL who received the 9 µg/kg dose in Study 302.

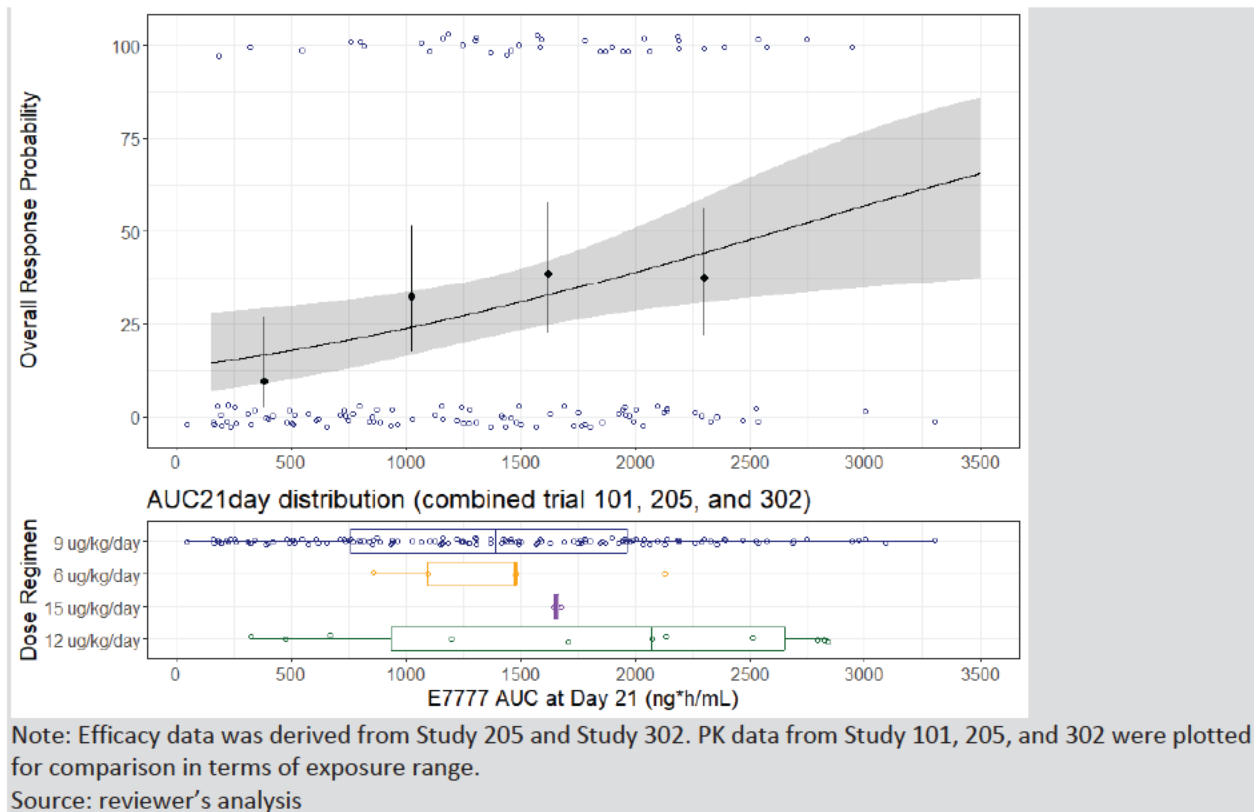
Figure 1: Predicted E7777 AUC vs. Best Observed Response (BOR) per Olsen Criteria Assessed by IRC.



Source: cpms-e7777-001r-v1, Figure 5

- The review team conducted additional, exploratory exposure-response analyses using data from Study 205 and Study 302 (Figure 2). The analyses suggested a positive relationship between ORR and AUC within the first cycle (AUC_{0-21day}). A consistent trend for E-R relationship was not observed for the other PK exposure measurements evaluated in the analysis.

Figure 2: Correlation Between ORR and AUC From Time 0 to 21 Days



6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data and The Applicant's Position:

The proposed dosing regimen was identified by evaluation of a range of doses in the Lead-In part of Study 302 and supported by the results of Study 101 and Study 205. The eligibility criteria of Study 302 ensured the study subject population was consistent with the general patient population for which the indication is being sought. The efficacy and safety of E7777 at a dose of 9 $\mu\text{g}/\text{kg}/\text{day}$ by IV infusion (days 1-5 of each 21-day cycle), are demonstrated by the results of Study 302 and supported by the results of Study E7777-J081-205 (Study 205) and Study 101, as described in Section 8 of this document.

The proposed dosing regimen is appropriate for the general patient population for which the indication is being sought.

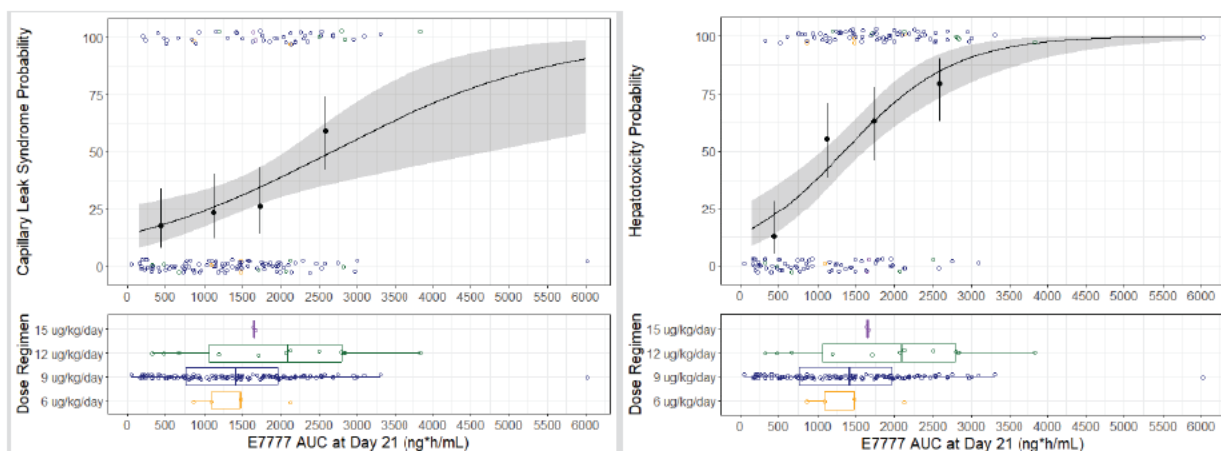
The FDA's Assessment:

The clinical pharmacology review team agrees that the recommended dose of 9 µg/kg is appropriate for the general population of adult patients with relapsed or refractory stage I-III CTCL.

The review team evaluated the potential benefit of an alternative dosage (e.g., 6 µg/kg or 12 µg/kg) as compared to the proposed recommended dosage of 9 µg/kg.

- The available data does not support a thorough characterization of the exposure-response relationships for efficacy due to uncertainties with the limited data at dosages other than 9 µg/kg. While a trend for a positive association and a shallow exposure-response curve was observed between early exposure and ORR, the predicted marginal increase in response rate at higher dose levels cannot be verified by the limited data at 12 µg/kg or higher. The predicted response rate at the 6 µg/kg dose level can be biased due to the small number of patients and the large PK variability observed in these patients.
- In 161 patients from Studies 101, 205, and 302, positive exposure-response relationships were identified between E7777 exposures ($C_{max,24h}$, AUC_{24h} , or AUC_{21d}) and adverse events of special interest including CLS and hepatotoxicity (Figure 3; also refer to Section 19.4). An increase in E7777 dose from 9 µg/kg to 12 µg/kg is predicted to substantially increase the probability of CLS and hepatotoxicity. The exposure-response analyses for safety does not provide evidence favoring the 6 µg/kg dose as the limited number of patients receiving 6 µg/kg dose showed comparable PK exposures to those at 9 µg/kg.

Figure 3: Correlation Between AUC From Time 0 to Day 21 and the Probability of CLS or Hepatotoxicity



Source: reviewer's analysis

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data and The Applicant's Position:

E7777 PK was not affected by a range of variables, as described in the Therapeutic Individualization section. There is no requirement for an alternative dosing regimen or management strategy for subpopulations based on intrinsic patient factors.

The FDA's Assessment:

The clinical pharmacology review team agrees that an alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors.

Population pharmacokinetics analyses showed a lack of impact by intrinsic factors, including age (23 to 86 years), sex, race (51% White, 12% African American/Black, 32% Asian), ECOG status (0 to 2), albumin (24-49 g/L), creatinine clearance (CLCr >24 mL/min), or mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN, or total bilirubin 1 to 1.5 times ULN and any AST), on the measured exposure of E7777 (refer to Section 19.4.x). The volume of distribution and clearance of denileukin diftitox-cxdI increase with increasing body weight (39 kg to 148 kg).

There was limited data in patients with severe renal impairment (n=2, CLCr ≥15 and <29 mL/min), but these patients had similar exposures as patients with normal renal function. There is no data in patients with moderate or severe hepatic impairment. However, dedicated PK studies in patients with severe renal impairment or moderate or severe hepatic impairment are not required given that E7777 is not expected to be substantially eliminated via the hepatic or renal pathways. The conclusion is based on the following information:

- 1) E7777 is a fusion protein and is expected to be eliminated by catabolic pathways.
- 2) In preclinical studies, denileukin diftitox was metabolized by proteolytic degradation and excreted as low molecular weight breakdown products.
- 3) Population PK analysis on clinical data did not suggest a statistically significant impact on E7777 exposure by creatinine clearance ranging from 24 to 369 mL/min. In the two patients with CLCr less than 30 mL/min, the predicted PK exposures were comparable to those in patients with normal renal function.

Additionally, dose adjustment based in immunogenicity or CD25 expression is not requirement.

Impact of Immunogenicity on PK, efficacy, and safety

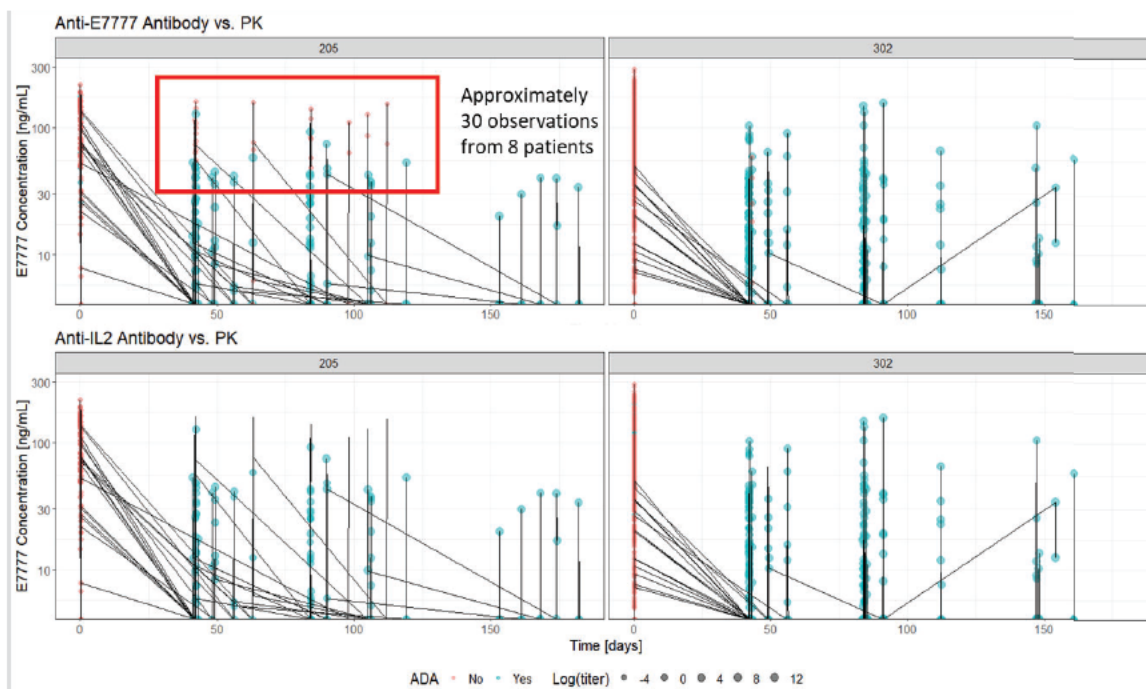
The presence of anti-drug antibodies is associated with a decrease in the measured, serum E7777 concentration.

- In Study 302, intensive PK data were collected in 20 patients who received the 9 µg/kg dose and analyzed by non-compartmental analysis. Almost 95% (18/19) of the ADA evaluable patients were positive for pre-existing anti-E7777 antibodies. Cycle 1 Day 1 PK parameters from patients who were negative for pre-existing anti-E7777 antibodies were slightly above

the median value as compared to patients who were positive. All 16 patients with reportable PK data by Cycle 3 Day 1 were positive for anti-E7777 antibodies and had increased titer values. The average C3D1/C1D1 ratio on Cmax and AUC for these patients was 0.47 and 0.32, respectively, suggesting a potential association between increased ADA titer and a decrease in the measured serum E7777 concentration.

- In Study 205, 8 patients were negative for anti-E7777 antibodies throughout the course of treatment. E7777 concentrations were relatively higher in these patients as compared to patients with at least 1 observation of positive anti-E7777 antibodies (Figure 4 upper left panel red box), which implies that the formation of anti-E7777 antibodies is associated with a decrease in the measured serum E7777 concentration.
- The effect of anti-IL2 antibody on E7777 PK is inconclusive due to limited observations from patients who were included in the PK analysis datasets and identified as negative for anti-IL2 antibody.

Figure 4: Individual E7777 Plasma Concentration Over Time Stratified by ADA Status



Source: reviewer's analysis

Available data does not suggest an adverse impact on safety or efficacy from ADA.

- In the Study 302 primary efficacy dataset, ORR in patients who were positive for pre-existing anti-E7777 antibody (17/51, 33%, 90% CI [22.5%, 45.7%]) was numerically lower than that in patients considered negative (6/14, 42.8%, 90% CI [20.6%, 67.5%]). However,

the comparison should be interpreted with caution given the small sample size for patients considered ADA negative at baseline and the overlapping confidence interval. Only 3 out of the 18 patients who were considered negative or not reportable at baseline remained as negative by Cycle 2 Day 1. All responders developed anti-E7777 antibodies during treatment. In the integrated exposure-response analysis for efficacy, the presence of anti-E7777 antibodies does not have an impact on efficacy (refer to Section 19.4.2).

- In the Study 302 primary efficacy dataset, only a small portion of reportable patients were positive at baseline for anti-IL2 antibodies (3/65) or were considered negative by Cycle 2 Day 1 (4/54). The small number of patients without treatment emergent ADA precludes direct comparisons of the response rates in patients with different ADA status. In the integrated exposure-response analysis, the presence of anti-IL-2 antibody is not negatively associated with odds of overall response.
- In the integrated exposure-response analysis, ADA was not positively correlated with safety outcomes.

Impact of CD25 expression on efficacy (b) (4)

The Applicant performed ad hoc analyses investigating the impact of categories of CD25 expression ($\geq 20\%$ to $< 40\%$ (N=19), $\geq 40\%$ to $< 60\%$ (N=23), and $\geq 60\%$ (N=26)) on ORR within the primary efficacy analysis set. The Applicant's analyses showed ORRs of 42.1% (N=8), 13.0% (N=3), and 53.8% (N=14) in the CD25 expression categories, respectively. Additional FDA analyses utilizing different categorical cutoffs suggest that the lower response rates seen in patients with CD25 expression between 40% and 60% may be an artifact of the selected cutoffs. Additionally, there is no biological rationale to support a relationship between intermediate CD25 expression and reduced efficacy.

The FDA also performed additional exploratory analyses on the intrasubject variability of CD25 expression and the potential impact of measuring CD25 expression to determine eligibility for E7777. Of the 68 patients in the primary efficacy analysis set, 17 patients had multiple biopsies with CD25 expression measured (2 measurements in 16 patients and 3 in 1 patient). Of those 17 patients, 2 (12%) had CD25 expression in one sample that was below the cutoff of $> 20\%$ CD25 expression, and one of the patients achieved a CR. The Applicant's report provides additional support based on 36 patients taking ONTAK that had skin biopsies with CD25 expression $< 20\%$ by IHC and found an overall response rate of 30.6%, which is similar to the results in Study 302. Taken together, these results suggest that measurements of CD25 expression by IHC are variable within patients and that response to E7777 was seen even in patients with CD25 expression below 20%, (b) (4)

For additional information on the assessment of CD25 expression, see Section 4.4.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data and The Applicant's Position:

E7777 is a biological therapy administered by IV infusion. Food-drug interactions are not relevant, and no clinically relevant drug-drug interactions are anticipated.

The FDA's Assessment:

The clinical pharmacology review team agrees that E7777 is not expected to have relevant food-drug or drug-drug interactions.

X

X

Primary Reviewer

Team Leader

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Table 4: Listing of Clinical Trials Relevant to this BLA

Study ID Design NCT No.	Diagnosis Inclusion Criteria	Number of Study Centers (Locations)	Study and Control Drugs Dose, Route, Regimen	Primary Study Objective	# Subjects	Duration	M/F Median age (Range)	Primary Endpoints
E7777-G000-302 Lead-In part Dose selection (CRM) Multicenter, open-label, single-arm NCT01871727	Recurrent or persistent CTCL	5 sites (US); 1 site (Australia)	E7777 IV infusion QD; Days 1 to 5 of each 21-day cycle. Starting dose 6 µg/kg/day, escalated stepwise (6, 9, 12, and 15 µg/kg/day)	To establish the MTD of E7777 and to select the dose of E7777 to be used in the Main part of Study 302	21 (All dose cohorts combined). 9 µg/kg: n=5 (Stage I-III), and n=3 (Stage IV)	Up to 8 21-day cycles ^a	10M, 11F 63.0 (26, 84)	DLTs and MTD

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftiox)

Table 4: Listing of Clinical Trials Relevant to this BLA

Study ID Design NCT No.	Diagnosis Inclusion Criteria	Number of Study Centers (Locations)	Study and Control Drugs Dose, Route, Regimen	Primary Study Objective	# Subjects	Duration	M/F Median age (Range)	Primary Endpoints
E7777-G000-302 Main Study Multicenter, open-label, single-arm NCT01871727	Recurrent or persistent CTCL	17 sites (US); 3 sites (Australia)	E7777 9 µg/kg/day IV infusion QD; Days 1 to 5 of each 21-day cycle.	To demonstrate efficacy of E7777 in subjects with recurrent or persistent Stage I to III CTCL, as assessed by ORR, according to GRS Olsen (2011).	91 (9 µg/kg dose only), n=64 (Stage I-III), n=26 (Stage IV), n=1 (no study drug)	Up to 8 21-day cycles per protocol, treatment could be continued at physicians discretion	Primary Efficacy Analysis Set: 45M, 24F 64.0 (28, 87) Full Analysis Set: 61M, 37F 65.0 y (28, 87)	ORR per IRC
E7777-J081-205 Multi-center, single-arm NCT02676778	Relapsed or refractory PTCL and CTCL.	20 sites (Japan)	E7777 9 µg/kg/day IV infusion QD; Days 1 to 5 of each 21-day cycle.	To evaluate efficacy of E7777 with ORR in subjects with relapsed or refractory PTCL and CTCL	CTCL: 19 PTCL: 17 Overall: 36	Up to 8 21-day cycles	Overall: 25M, 11F 64.5 y (27, 82)	ORR per IRC
E7777-J081-101 Multi-center,	PTCL (including CTCL in a	5 sites (Japan)	E7777 IV infusion QD Days 1 to 5 of each 21-day cycle.	To determine MTD for E7777 based on observed DLTs	CTCL: 3 PTCL: 10 Total: 13	Up to 8 21-day cycles	Total: 8M, 5F	DLTs and MTD

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftotox)

Table 4: Listing of Clinical Trials Relevant to this BLA

Study ID Design NCT No.	Diagnosis Inclusion Criteria	Number of Study Centers (Locations)	Study and Control Drugs Dose, Route, Regimen	Primary Study Objective	# Subjects	Duration	M/F Median age (Range)	Primary Endpoints
open-label, dose-escalation NCT01401530	broad definition).		Starting dose 6 µg/kg/day, escalated stepwise (6, 9, and 12 µg/kg/day).				64.0 y (23, 75)	
CR = complete response, CTCL = cutaneous T-cell lymphoma, CRM = continual reassessment method, DLT = dose limiting toxicity, EORTC = European Organisation for Research and Treatment of Cancer, FAS = full analysis set, GRS = Global Response Score, ICSL = International Society for Cutaneous Lymphomas, IRC = independent review committee, IV = intravenous, MTD = maximum tolerated dose, NCT = national clinical trial, ORR = objective response rate, PR = partial response, PTCL = peripheral T-cell lymphoma, QD = once daily. For Study 302, the FAS was defined as all subjects (both Main Study [N = 90] and Lead-In [N = 8]) who received study drug at the 9 µg/kg dose. For Study 302, the Primary Efficacy Analysis Set was defined as all Stage I to III CTCL subjects (both Main Study [N = 64] and Lead-In [N = 5]) who received study drug at the 9 µg/kg dose. Study 302 ORR = CR and PR according to ISCL/EORTC GRS (Olsen, et al., 2011.) Study 205 ORR = CR and PR according to Cheson, et al., 2007; ORR for subjects with CTCL was also assessed according to Olsen, et al., 2011.								

The Applicant’s Position:

Study 302 and the supportive Studies 101 and 205 provide adequate data to evaluate the efficacy and safety of E7777 in subjects with recurrent or persistent CTCL.

The FDA’s Assessment:

The FDA agrees with the Applicant’s position.

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study E7777-G000-302

Trial Design

The Applicant's Description:

Study E7777-G000-302 (Study 302) was a multicenter, open label, single arm study of E7777 in adult subjects with recurrent or persistent CTCL (MF or SS, with CD25 expression of $\geq 20\%$) who had received at least 1 prior systemic CTCL therapy. The study consisted of an initial Lead-In part followed by the Main Study. In the Lead-In part, a continual reassessment method was used to establish the maximum tolerated dose (MTD) of E7777 and to select the dose of E7777 to be used in the Main Study. A total of 21 subjects were treated at doses ranging from 6 $\mu\text{g}/\text{kg}/\text{day}$ to 15 $\mu\text{g}/\text{kg}/\text{day}$. The Main Study evaluated the efficacy and safety of E7777 at the dose selected based on results of the Lead-In part (9 $\mu\text{g}/\text{kg}/\text{day}$). A sufficient number of subjects in the Main Study were recruited so that, when combined with subjects in the Lead-In part, a total of approximately 70 subjects with recurrent or persistent Stage I to III CTCL were treated with E7777 9 $\mu\text{g}/\text{kg}/\text{day}$ to assess efficacy.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint was objective response per Independent Review Committee (IRC) assessment based on Global Response Score (GRS; Olsen, et al., 2011).

The secondary efficacy endpoints for the Main Study were:

- Duration of response (DOR) based on GRS
- Time to response (TTR) based on GRS
- ORR assessed by investigator using GRS (Olsen, et al., 2011)
- Objective response assessed by IRC using Prince (Prince, et al., 2010)
- Skin response according to the modified Severity Weighted Assessment Tool (mSWAT)
- Duration of skin response
- Time to skin response

Exploratory efficacy endpoints included PFS, clinical benefit rate (CBR), time to progression (TTP), pruritus improvement, and health-related QoL endpoints.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Sample size: The sample size of approximately 70 Stage I to III subjects (including subjects from both the Main Study and the Lead-In part combined) was estimated assuming that the lower limit of the 2-sided 95% CI of ORR exceeding 25% indicates clinical benefit in persistent or recurrent CTCL, i.e., an ORR of at least 36%.

Analysis Populations:

- Full Analysis Set (N = 98): All subjects who received E7777 9 µg/kg from Lead-In part and Main Study (Figure 1).
- Primary Efficacy Analysis Set (N = 69): All subjects with Stage I to III CTCL (both Main Study and Lead-In part) who received E7777 9 µg/kg (Figure 1).
- Investigator Stage I to III Efficacy Analysis Set (N = 71): All subjects with Stage I to III CTCL (both Main Study and Lead-In part) who received E7777 9 µg/kg. Baseline CTCL disease stage was per investigator assessment on the eCRF. This analysis set is the same as the Primary Efficacy Analysis Set except for 2 additional subjects, for whom the IRC determined there was visceral disease at Baseline that was not identified by the investigator, categorizing the disease stage as Stage IV.
- Safety Analysis Set (N = 98): All subjects who received E7777 9 µg/kg from Lead-In part and Main Study.
- Stage I to III Safety Analysis Set (N = 69): All subjects with Stage I to III CTCL (both Main Study and Lead-In part) who received E7777 9 µg/kg.
- PK Analysis Set: All subjects who received E7777 9 µg/kg (both Main Study and Lead-In part) from whom at least 1 quantifiable concentration of E7777 was observed (N = 94).
- Population PK Analysis Set: All subjects from whom at least 1 quantifiable concentration of E7777 was available with a documented dosing history from both Lead-In part and Main Study (N = 105).
- Population PK/PD Analysis Set: All subjects from both Lead-In part and Main Study in the Population PK Analysis Set for whom efficacy (N = 64) and safety (N = 104) variables were also available.

Primary Efficacy Endpoint Analysis: For ORR, the 2-sided, exact 95% CI was calculated using the Clopper-Pearson method. Treatment was to be considered efficacious and demonstrating clinical benefit if the lower bound of the 2-sided 95% CI of the ORR exceeded 25%.

Secondary Efficacy Endpoint Analysis:

DOR and TTR for subjects with confirmed CR or PR were analyzed using Kaplan-Meier (KM) product-limit estimates. The median and quartiles were provided with 95% CIs, if estimable. ORR for skin response, based on the mSWAT score, was defined as the proportion of subjects with best skin response of (confirmed) CR or PR.

The DOR and TTR for skin response were analyzed following the same approach for the secondary endpoints DOR and TTR.

Exploratory Efficacy Endpoint Analysis

PFS and TTP for E7777 were calculated using KM product-limit estimates and plotted over time. The medians and their corresponding 2-sided 95% CIs were provided.

CBR was defined as the proportion of subjects that had best overall response (BOR) of CR or PR or durable stable disease (SD) (≥ 23 wks). Durable SD must have been achieved at least 23 weeks after first dose of study drug.

Subject's pruritus improvement rate was calculated with a 2-sided exact 95% CI using the Clopper-Pearson method. In addition, the percentages of subjects who had at least 20% and at least 50% improvements (decreases) relative to baseline in each of the visual analog scale-based assessment scores were tabulated.

ORR in subjects who received and who did not receive steroid medication was summarized along with the 2-sided exact 95% CI using the Clopper-Pearson method.

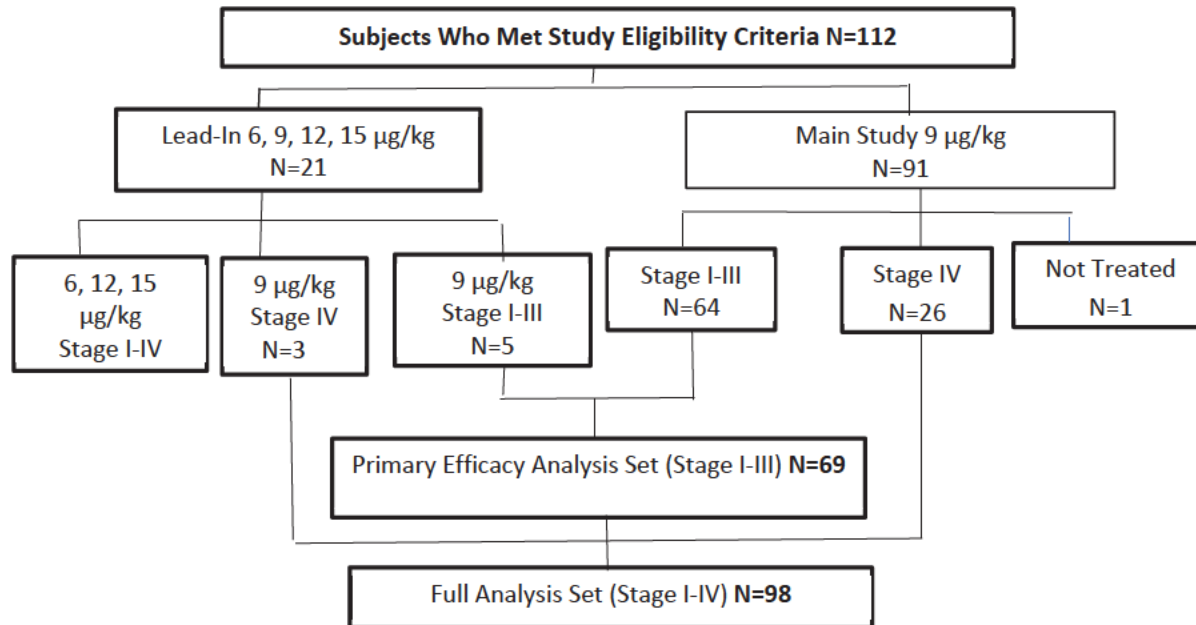
Safety Analysis: Safety data were summarized using descriptive statistics (e.g., n, mean, standard deviation (StDev), median, first quartile (Q1), third quartile (Q3), minimum (Min) and maximum (Max) for continuous variables; number and percentage for categorical variables). Safety data included AEs, clinical laboratory results, vital signs, and ECGs.

PK Analysis: Serum concentration data for E7777 were analyzed and summarized using descriptive statistics (n, mean, StDev, median, and Min and Max) by time point. PK parameters were derived for subjects with serial blood PK sampling using noncompartmental analysis for E7777 on Day 1 of Cycles 1, 3, and 5. Serum concentration data from the sparse PK sampling time points and the intense PK sampling time points were analyzed using a population PK approach.

PK/PD analysis: The relationship of E7777 exposure and key efficacy and safety endpoints was assessed.

Immunogenicity Analysis: Anti-E7777/anti-IL-2 antibodies results and neutralizing anti-E7777/IL-2 antibodies results (positive/negative) were summarized by number of subjects and percentage by visit. Titer levels were summarized using descriptive statistics (n, mean, StDev, Q1, Q3, median, and Min and Max) by visit.

Figure 5: Subjects Who Met Eligibility Criteria in Study E7777-G000-302



The FDA’s Assessment:

The FDA concurs with the Applicant’s assessment.

Protocol Amendments

The Applicant’s Description:

The Study E7777-G000-302 protocol was amended 6 times (Table 5).

Table 5: Study E7777-G000-302 Protocol Amendments

Amendment (date)	Significant Changes to the Protocol
Amendment 01 (17 Apr 2013)	Addition of a nonformal interim analysis to ensure that an acceptably safe dose was established and at least 1 OR was recorded in the Lead-In part of the study before proceeding into the Main part of the study where larger numbers of subjects were to be studied. Process was added for mSWAT score, data collection for tumor assessment by Prince, including photographs. Subjects with visceral involvement were allowed in the Lead-In part of the study, inclusion criterion #4 was corrected, and the “Exclusion criteria” list was updated to exclude subjects with CNS involvement. Visceral disease assessment was added.

Table 5: Study E7777-G000-302 Protocol Amendments

Amendment (date)	Significant Changes to the Protocol
Amendment 02 (22 Apr 2014)	The DLT definition for “serious infusion reaction” was revised to allow the opportunity to assess if steroid premedication was effective in managing Grade 3 infusion reaction. The DLT definition for CLS was changed to be based on CTCAE grading for consistency in assessment of DLT and current standard practice for managing toxicity. Dose interruption and dose modification instructions were revised for consistency with changes in DLT definitions. The exclusion criterion “need for treatment with a drug that contains a warning for hepatotoxicity or nephrotoxicity in its labeling” was removed. Investigator-assessed tumor responses will be used for decision-making in the Main Study.
Amendment 03 (20 Apr 2016)	The E7777 dose for the Main Study was stated as 9 µg/kg, (after completion of the Lead-In part). CTCL disease stage for subject inclusion in the Main Study now allowed Stage IVA₁ but excludes lymph node disease N₂, N₃, to align with subject population in the reference ONTAK study (L4389-11). Tumor assessment method description and schedules were revised to align with changes in CTCL disease stage included. Drug administration instructions for a new lyophilized formulation of E7777 is added.
Amendment 04 (26 Jun 2017)	The inclusion criterion concerning CTCL disease stage for subject inclusion in the Main Study allowed Stages IA to IVA₂, including lymph node disease N₂ and N₃. The biopsy and histologic characterization requirements were updated for the Screening Period of the Main Study to include disease staging for the subjects with N₂/N₃. The schedule of CT scans was modified to include additional required CT scans every 3 cycles (±1 week) during treatment for subjects with N₂, N₃, and N_x, as well as ¹⁸FDG PET-CT scans. The exclusions of known involvement of the bone marrow and CTCL disease with CNS involvement were removed from eligibility for the Main Study. The exclusion criterion concerning active malignancy other than CTCL was changed from excluded within 2 years instead of 5 years. Biopsy of suspicious lymph nodes during screening was strongly recommended. The exclusion criterion concerning significant infections was updated to specify infections requiring systemic anti-infective therapy. Statistical detail regarding analysis of skin responses, and definition of DOR were added. Treatment continuation beyond 8 cycles was allowed for subjects with skin tumor response and who were deriving clinical benefit from E7777 treatment instead of objective tumor response. The requirement of a visual acuity test was removed, as the results from the Lead-In part of the study were deemed as sufficient. Appendix 4 updated to indicate: “only N3 is considered as nodal disease for GRS.” Appendix 5 updated to add Charter for lymph node disease assessment.
Amendment 05 (03 May 2018)	Inclusion criterion concerning screening assessments and tumor assessment methods and schedule was updated with the removal of language referring to the skin (in the context of CD25 expression) and replaced with a general reference to “tumor”. CPK monitoring was added as a procedure. The CTCAE criteria was updated from v4.03 to v5.0. Guidelines for ECG monitoring were revised to reduce ECG monitoring based on Lead-In part data analysis, ONTAK safety profile, and E7777 clinical experience

Table 5: Study E7777-G000-302 Protocol Amendments

Amendment (date)	Significant Changes to the Protocol
Amendment 06 (29 Oct 2019)	The exploratory objective QoL was updated to include Stages I to III subjects. Stages I to III subjects were included in the evaluation of efficacy and safety for the Main Study and Stages I to III Lead-In subjects from the 9 µg/kg dose group. Stages I to III subjects are to be used for the primary efficacy analysis. The target number of Stages I to III subjects was updated for a total of approximately 70 Stages I to III subjects from the Lead-In and Main parts of the study combined. The immunogenicity assessment of evaluation of positive anti-IL-2 immunogenicity samples after treatment with E7777 was updated to be carried out for 3 years or until samples are negative. Stages I to III subjects were to be used for the primary efficacy analyses; safety analyses for the main part of the study were to be performed in all subjects, and Stages I to III subjects separately. The criteria for follow-up of subjects with immunogenicity were clarified, so that immunogenicity would be followed up in subjects who developed PD since they were exposed to E7777. Updated definition of primary efficacy evaluation set and primary efficacy evaluation analysis to Stage I-III CTCL only. Safety analysis set in Main Study to include all subjects and have a separate analysis set for Stage I-III subjects.

CLS = capillary leak syndrome, CNS = central nervous system; CPK = creatine phosphokinase, CT = computed tomography, CTCAE = Common Terminology Criteria for Adverse Events, CTCL = cutaneous T-cell lymphoma, DLT = dose-limiting toxicity, ECG = electrocardiogram, ¹⁸FDG PET-CT = ¹⁸fluorodeoxyglucose positron emission tomography-computed tomography, IL-2 = interleukin-2, OR = objective response; PD = progressive disease, QoL = quality of life.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

8.1.2. Study Results for E7777-G000-302

Compliance with Good Clinical Practices

Data and The Applicant's Position:

Study 302 was performed in full compliance with ICH and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation is archived as required by regulatory authorities.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Financial Disclosure

Data:

No clinical investigators in Study 302 (Lead-In part and Main Study) had significant disclosable financial arrangements (i.e., none >\$25,0000). A list of investigators can be found in Module 1.3.4 Financial Certification and Disclosure documents. Details of financial disclosure are presented in Section 19.2.

The Applicant's Position:

As the sponsor of Study 302, Eisai has adequately disclosed any financial interests or arrangements with clinical investigators in accordance with the guidance for industry.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Patient Disposition

Data:

In the Lead-In part of the study, 36 subjects were screened; 21 subjects (58.3%) continued in the study, and 15 subjects (41.7%) failed screening. In the Main Study, 143 subjects were screened, 52 subjects (36.4%) failed screening and 91 subjects (63.6%) were enrolled into the study. Of the 91 subjects enrolled in the Main Study, 1 subject (0.7%) did not receive E7777 treatment (hospitalized due to a serious AE (SAE), before first dose received, then withdrawn). The reasons for treatment discontinuation of subjects in both the Primary Efficacy Analysis Set (N=69) and the Full Analysis Set (N=98) are summarized in Table 6. In the Primary Efficacy Analysis Set, 79.7% of subjects discontinued study drug for reasons other than completing 8 cycles.

Table 6: Subject Disposition and Reasons for Treatment Discontinuation in Study E7777-G000-302		
	Primary Efficacy Analysis Set E7777 9 µg/kg (N=69) n (%)	Full Analysis Set E7777 9 µg/kg (N=98) n (%)
Treated	69 (100.0)	98 (100.0)
Treatment ongoing at data cutoff date	2 (2.9)	2 (2.0)
Treatment completed as required per protocol	12 (17.4)	14 (14.3)
Discontinued treatment	55 (79.7)	82 (83.7)
Primary reason for discontinuation from study treatment		
Disease progression	21 (30.4)	30 (30.6)
Clinical progression	7 (10.1)	11 (11.2)
Adverse event	7 (10.1)	12 (12.2)
Subject choice	7 (10.1)	12 (12.2)
Lost to follow-up	1 (1.4)	1 (1.0)
Administrative/Other	12 (17.4)	16 (16.3)
Withdrawal of consent	6 (8.7)	7 (7.1)
Other	6 (8.7)	9 (9.2)
Completed treatment or discontinued from treatment but on survival follow-up at data cutoff date	5 (7.2)	5 (5.1)

As reported on the Subject Disposition (Treatment Phase) CRF.

The Applicant's Position:

The number of subjects enrolled was consistent with the planned sample size. The main reasons for discontinuation of treatment were disease progression (21 subjects [30.4%]), clinical progression (7 subjects [10.1%]), and AE (7 subjects [10.1%]).

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.]

Protocol Violations/Deviations

Data:

Although a number of minor deviations from the protocol (e.g., missed visits) occurred, these deviations were not considered to have affected the evaluation of efficacy or safety. None of

the subjects received the incorrect treatment. No major protocol deviations per protocol were reported during this study. No major protocol deviations related to COVID-19 were reported.

The Applicant’s Position:

There were no major protocol deviations that impacted data quality.

The FDA’s Assessment:

The FDA concurs with the Applicant’s assessment.

Table of Demographic Characteristics

Data:

A summary of subject demographic characteristics is presented in Table 7.

Table 7: Demographic and Baseline Characteristics of Subjects: Study E7777-G000-302		
Category	Primary Efficacy Analysis Set E7777 9 µg/kg (N=69)	Full Analysis Set E7777 9 µg/kg (N=98)
Age (year) ^a		
Mean (StDev)	62.0 (12.45)	62.9 (11.91)
Median (Min, Max)	64.0 (28, 87)	65.0 (28, 87)
Age group (years) ^a , n (%)		
<65 years	35 (50.7)	48 (49.0)
≥65 years	34 (49.3)	50 (51.0)
Sex, n (%)		
Male	45 (65.2)	61 (62.2)
Female	24 (34.8)	37 (37.8)
Ethnicity, n (%)		
Hispanic or Latino	10 (14.5)	14 (14.3)
Not Hispanic or Latino	57 (82.6)	81 (82.7)
Missing	2 (2.9)	3 (3.1)
Race, n (%)		
White	50 (72.5)	73 (74.5)
Black or African American	13 (18.8)	16 (16.3)
Asian (non-Japanese)	1 (1.4)	1 (1.0)
Other	4 (5.8)	7 (7.1)

Table 7: Demographic and Baseline Characteristics of Subjects: Study E7777-G000-302		
Category	Primary Efficacy Analysis Set E7777 9 µg/kg (N=69)	Full Analysis Set E7777 9 µg/kg (N=98)
Missing	1 (1.4)	1 (1.0)
Country, n (%)		
Australia	12 (17.4)	14 (14.3)
United States	57 (82.6)	84 (85.7)
ECOG Performance status, n (%)		
0	39 (56.5)	53 (54.1)
1	30 (43.5)	45 (45.9)

ECOG = Eastern Cooperative Oncology Group, Max = maximum, Min = minimum, StDev = standard deviation.
a: Age is calculated at the date of informed consent.

The Applicant’s Position:

Demographic characteristics of subjects in Study 302 were broadly consistent with the target population of patients with persistent or recurrent CTCL.

The FDA’s Assessment:

The FDA concurs with the Applicant’s assessment.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

The study enrolled subjects with CTCL with both early stage and advanced disease, Stages I to IV. Subjects with Stage IV disease were excluded from the primary efficacy analysis set to match the population of ONTAK Study 11. Of the 69 subjects in the Primary Efficacy Analysis Set, 30 (43.5%) had earlier stage (Stage IA/IB/IIA) disease, 24 (34.8%) had Stage IIB disease (subjects with T3 skin tumors), and 15 (21.7%) had Stage IIIA/IIIB disease (subjects with skin erythroderma [T4]; Table 8). Regarding the type of CTCL, 66 subjects (95.7%) had MF, and 3 subjects (4.3%) had SS. No subjects in the Primary Efficacy Analysis Set had nodal disease (N3) at baseline, which is classified as Stage IV.

Category	E7777 9 µg/kg (N=69)
CTCL type, n (%)	
MF	66 (95.7)
SS	3 (4.3)
CTCL disease stage at study entry, n (%)	
IA/IB/IIA	30 (43.5)
IIB	24 (34.8)
IIIA/IIIB	15 (21.7)

CTCL = cutaneous T-cell lymphoma, IRC = Independent Review Committee, MF = mycosis fungoides, SS = Sézary syndrome.

All subjects in the study (100%) received at least 1 prior anti-CTCL therapy, as defined by the protocol. The median number of prior anticancer therapies in the Primary Efficacy Analysis Set was 4.0. Forty-five subjects (65.2%) in the Primary Efficacy Analysis Set received 4 or more prior anticancer therapies, and the maximum number any 1 subject received was 18 (Table 9). The most common prior anticancer therapies are the mainstays of CTCL treatment, including photodynamic therapy (e.g., photopheresis, psoralen ultraviolet light A; 56.5%), total skin electron beam therapy (42.0%), and systemic retinoids and methotrexate/pralatrexate (49.3% each). A subset of subjects received newer systemic anticancer therapies that were not available during the ONTAK registration studies, including mogamulizumab (8 subjects [11.6%]), brentuximab vedotin (18 subjects [26.1%]), and HDAC inhibitor (24 subjects [34.8%]).

Category	Primary Efficacy Analysis Set E7777 9 µg/kg (N=69)
Subjects with any prior anticancer therapy ^a , n (%)	69 (100.0)
Number of prior anticancer therapies, n (%)	
Mean (StDev)	4.8 (2.99)
Median (Min, Max)	4.0 (1, 18)
Type of anticancer therapy ^b	
Photodynamic therapy	39 (56.5)
TSEBT	29 (42.0)
Retinoid	34 (49.3)

Table 9: Prior Anticancer Therapy: Study E7777-G000-302	
Category	Primary Efficacy Analysis Set E7777 9 µg/kg (N=69)
Methotrexate/Pralatrexate	34 (49.3)
Chemotherapy: Other systemic	12 (17.4)
Chemotherapy: Topical	20 (29.0)
Immune therapy: Interferon	23 (33.3)
Immune therapy: Other	14 (20.3)
HDAC inhibitor	24 (34.8)
Brentuximab Vedotin	18 (26.1)
Mogamulizumab	8 (11.6)
Transplantation	1 (1.4)
Investigational	13 (18.8)
Other	24 (34.8)
Radiation: Local	19 (27.5)
Other	7 (10.1)

Photodynamic Therapy includes PUVA, UVB, and ECP.

ECP = extracorporeal photopheresis, HDAC = histone deacetylase, Max = maximum, Min = minimum, PUVA = psoralen ultraviolet light A, StDev = standard deviation, TSEBT = total skin electron beam therapy, UVB = ultraviolet light B.

a: Including subjects with medication/ nonmedication.

b: Subjects may be counted in multiple categories.

The Applicant's Position:

All stages of CTCL, both early and late, were represented in the patient population in Study 302; only Stage I-III were included in the primary efficacy analysis to match as closely as possible the population in ONTAK Study 11.

The subjects in this study represent a relatively heavily pre-treated population.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

There was no significant noncompliance with the treatment regimen based on drug

accountability records. In the Study 302 Stage I to III Safety Set, the median number of infusions per cycle was 4.88, indicating that 5 doses per cycle were received in almost all cases. All 69 subjects (100.0%) took at least 1 concomitant medication in the Primary Efficacy Analysis Set. The types of concomitant medications were consistent with those expected for the mostly elderly study population of subjects with persistent or recurrent CTCL.

The required study premedications prior to each infusion of E7777 were acetaminophen, diphenhydramine, antiemetic agents, and hydration; hydration was at the discretion of the investigator. All subjects except one received the required study premedications.

In both the Lead-In part and Main Study, premedication with systemic steroids was not allowed, except in the event of grade ≥ 2 infusion reaction, per investigator judgment. A total of 12 subjects (17.4%) in the Primary Efficacy Analysis Set received a systemic steroid premedication, all for management of infusion reaction. Five of the 12 subjects received systemic steroids after Grade 2 or 3 infusion reaction experienced during the first day of treatment. The incidence of steroid premedication was highest in Cycles 1 to 3, after which the incidence decreased. There were no protocol-defined rescue medications.

The Applicant's Position:

There were no concerns relating to study drug compliance and compliance with required premedication. Other concomitant medications were consistent with those expected for the study population of subjects with persistent or recurrent CTCL.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The primary endpoint of Study 302 was ORR, defined as the proportion of subjects with a BOR of confirmed CR or PR based on GRS, by IRC and per Olsen, et al., 2011 criteria. In the Primary Efficacy Analysis Set, 25 of 69 subjects achieved an objective response, giving an ORR of 36.2% (95% CI: 25.0%, 48.7%). Six subjects (8.7%) achieved a complete response (CR) (Table 10).

	IRC (Olsen et al 2011) (N=69)	Investigator Assessed (Olsen et al 2011) (N=71)
Objective response rate (CR + PR), n (%)	25 (36.2)	30 (42.3%)
95% CI	(25.0, 48.7)	(30.6%, 54.6%)

Table 10: Summary of Objective Response Rate E7777 9 µg/kg: Study E7777-G000-302		
	IRC (Olsen et al 2011) (N=69)	Investigator Assessed (Olsen et al 2011) (N=71)
Best overall response from GRS, n (%)		
Complete response (CR)	6 (8.7)	6 (8.5)
Partial response (PR)	19 (27.5)	24 (33.8)
Stable disease	36 (52.2)	33 (46.5)
Progressive disease	3 (4.3)	4 (5.6)
Unknown	5 (7.2)	4 (5.6)

IRC assessments are based on the Primary Efficacy Analysis Set. Investigator assessments are based on the Investigator Stage I to III Efficacy Analysis Set. For best overall responses using Olsen, et al., 2011, PR and CR must be confirmed at least 3 weeks after initial assessment of response. SD must be ≥ 3 weeks after 1st dose to be considered as best overall response. CI = confidence interval, CCR = clinical CR, GRS = Global Response Score, IRC = Independent Review Committee.

The Applicant’s Position:

The ORR results in Study 302 demonstrate the efficacy of E7777 in subjects with persistent or recurrent CTCL.

The FDA’s Assessment:

The FDA concurs with the Applicant’s assessment. Note that the FDA assessment of efficacy is based on the evaluation by the independent review committee.

Data Quality and Integrity

Data:

Quality and integrity of study data were assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in the Study 302 protocol.

The Applicant’s Position:

There are no concerns relating to data quality and integrity.

The FDA’s Assessment:

The FDA concurs with the Applicant’s assessment.

Efficacy Results – Secondary and other relevant endpoints

Data:

Other efficacy results, including for secondary endpoints and other relevant (exploratory)

endpoints, are:

- ORR (95% CI) by investigator assessment in the Investigator Stage I to III Efficacy Analysis Set was 42.3% (30.6%, 54.6%) (30 of 71 subjects), with 8.5% (6 subjects) achieving a CR.
- Median TTR was 1.41 months. The majority of responders (68% and 70% by IRC and investigator assessments, respectively) achieved a response after 1 to 2 cycles of treatment.
- Responses were accompanied by a decrease in skin tumor burden, including about one-third of subjects achieving skin tumor burden reduction of $\geq 80\%$, and 8 subjects with 100% clearance of skin lesions (CR) per IRC (Figure 2).
- Skin responses, a key secondary endpoint, were the same as GRS objective responses, for both IRC and investigator assessments.
- Results using the Prince response criteria (which was used in ONTAK Study 11) were similar to the primary efficacy results that used the Olsen, et al., 2011 criteria. For the Primary Efficacy Analysis Set, the ORR (95% CI) by IRC using the Prince, et al., 2010 criteria was 36.2% (25.0%, 48.7%) (25/69 subjects), and the CR rate 5.8% (4 subjects).
- CBR per IRC was 49.3% (95% CI: 37.0%, 61.6%) including 9 subjects with durable stable disease (SD).
- Pruritus improvement was observed during E7777 treatment in 31.7% of subjects who had a pruritus score of ≥ 20 at baseline (N=41).
- Overall, analyses demonstrated that QoL is maintained or improved during treatment with E7777.

Duration of response data are presented under “Durability of Response”

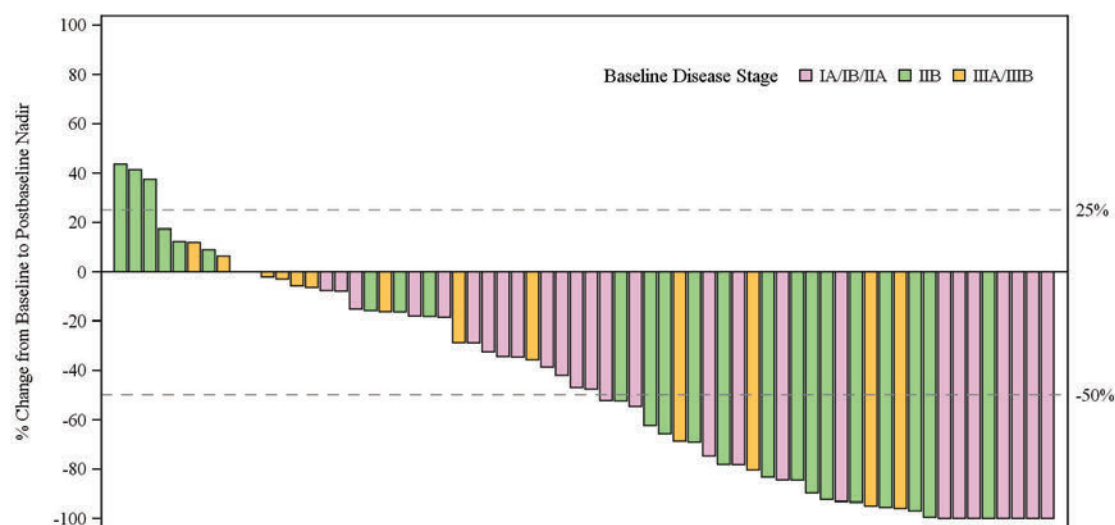


Figure 6: Waterfall Plot for Skin Tumor Burden (mSWAT Score) – Independent Review Committee Assessment – Primary Efficacy Analysis Set

This plot represents each subject's percent change in mSWAT score from baseline to postbaseline nadir.

Subgroup analyses of efficacy were conducted by baseline disease stage (IA/IB/IIA; IIB; IIIA/IIIB), age (<65; ≥65), sex and race. Analysis of ORR assessed by IRC for baseline disease stage subgroups in the Primary Efficacy Analysis Set (69 subjects) showed a higher proportion of responders among subjects in the subgroup category IA/IB/IIA (36.7%; 11/30 subjects) and IIB (45.8%; 11/24 subjects) as compared with the Stage IIIA/IIIB category (20%; 3/15 subjects). The Full Analysis Set included 29 additional subjects with Stage IV disease; ORR for these subjects was 6.9% (2 subjects). A similar pattern of results was observed for the secondary endpoints and for ORR analysis of the Investigator Stage I to III Efficacy Analysis Set. Subgroup analyses by age showed no notable difference between the age categories for any tumor response variable.

Post hoc analyses of efficacy by prior targeted systemic anticancer therapy (yes/no; e.g., romidepsin, brentuximab vedotin, or mogamulizumab) and by concomitant steroid therapy (yes/no) showed no notable effects of these variables on efficacy.

The Applicant's Position:

The secondary and exploratory efficacy results in Study 302 further demonstrate the efficacy of E7777 in subjects with persistent or recurrent CTCL.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Dose/Dose Response

Data and The Applicant's Position:

Not applicable. The Main Study part of Study 302 evaluated the efficacy of a single dose of E7777.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment. For the FDA's assessment of the recommended dose, see Section 6.2.2.

Durability of Response

Data:

The median (95% CI) DOR using KM estimates was not estimable (NE) among the 25 subjects in the Primary Efficacy Analysis Set who were responders due to censoring. Over half of the subjects, 13 (52.0%), had a DOR ≥ 6 months, and 5 (20.0%) had a DOR ≥ 12 months. The median observed DOR assessed by IRC in the Primary Efficacy Analysis Set was 6.47 months. The observed median DOR by investigator assessment was 5.68 months. A post-hoc sensitivity analysis of DOR was performed for Study 302 where new events were the first documentation of disease progression per GRS (Olsen, et al., 2011), progression based on the disposition eCRF, initiation of new anticancer therapy, or death from any cause, whichever occurs first (Figure 3). By this analysis, among the 25 subjects who were responders in the Primary Efficacy Analysis Set, the median (95% CI) DOR using KM estimates was 8.9 (5.0, NE) months. The median observed DOR remained as 6.47 months; 13 subjects (52.0%) had a DOR ≥ 6 months, and 5 subjects (20.0%) had a DOR ≥ 12 months.

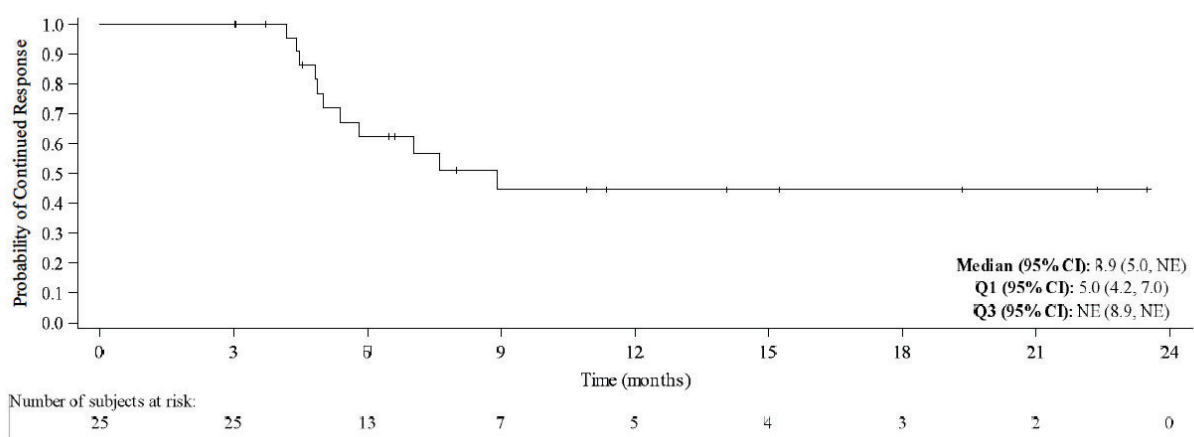


Figure 7: Kaplan-Meier Plot of Duration of Response - Independent Review Committee (IRC) Assessment per Olsen 2011 - Treating Disease Progression/Start of New Anticancer Therapy as Events – Primary Efficacy Analysis Set

Calculated for subjects with BOR of CR or PR for GRS. Duration of response in this sensitivity analysis is defined as the time from the date that a confirmed response was first documented as the evidence of complete response or partial response until the date of the first documentation of disease progression per GRS Olsen, progression based on disposition eCRF, initiation of new anticancer therapy, or death from any cause, whichever occurs first. The median is estimated using the KM method, and the 95% CI is constructed with a generalized Brookmeyer and Crowley method.

+: censored.

BOR = best overall response, CI = confidence interval, CR = complete response, eCRF = electronic case report form, GRS = Global Response Score, KM = Kaplan-Meier, NE = not estimable, PR = partial response, Q1 = first quartile, Q3 = third quartile.

The Applicant's Position:

Responses were durable based on data from observed DOR and from the sensitivity analyses.

The FDA's Assessment:

The median (95% CI) DOR using Kaplan-Meier (KM) estimate was not estimable (NE) due to 100% censoring. The proportion of responders at landmark timepoints (6 months and 12 months) were provided along with the range of DOR. Note that out of a total of 25

responders, 5 individual patients switched to subsequent therapy which may confound the DOR result. Nevertheless, in patients who achieved a response, the duration of response exceeded 6 months in 52% (13/25) and 12 months in 20% (5/25).

Persistence of Effect

Data and The Applicant's Position:

Not applicable. No persistence of effect data from Study 302 are submitted with this BLA.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Quality of life (QoL) was assessed using Functional Assessment of Cancer Therapy-General (FACT-G; increased score shows improvement) and Skindex-29 (decreased score shows improvement). The mean change from baseline in FACT-G Total Score gradually increased from Cycle 2 (0.9) to Cycle 4 (3.4) and this improvement was maintained through Cycle 8. The Skindex-29 Total Score decreased by 1.8 points at Cycle 2 and this improvement continued until an 8.3-point decrease was seen at Cycle 7. The responder analysis indicates that QoL improvement is driven by response to treatment, with responders having better results than nonresponders.

The Applicant's Position:

The improvement in QoL assessed by FACT-G and Skindex-29 in subjects in Study 302 support a clinical benefit of treatment with E7777, particularly in responders.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Additional Analyses Conducted on the Individual Trial

Data:

- An ad hoc analysis of ORR based on prior anticancer therapy was conducted, specifically on prior use of mogamulizumab, brentuximab, and HDAC inhibitors, which represent newer therapies, approved after ONTAK Study 11 was conducted. In the Primary Efficacy Analysis Set, ORR (95% CI) was 35.3% (19.7, 53.5) and 37.1% (21.5, 55.1) and CBR was 47.1% (29.8, 64.9) and 51.4% (34.0, 68.6) in 34 subjects who had or 35 subjects had not received prior treatment with at least 1 of these therapies, respectively.
- In a planned sensitivity analysis, ORR in subjects who received and who did not receive concomitant systemic steroid medication was determined in the Primary Efficacy Analysis

Set; ORR (95% CI) with or without concomitant steroids was similar, 36.0% (18.0, 57.5) and 36.4% (22.4, 52.2), respectively.

- An ad hoc analysis of ORR based on category of CD25 expression ($\geq 20\%$ to $< 40\%$, $\geq 40\%$ to $< 60\%$, and $\geq 60\%$) was conducted. No major differences in CD25 expression level were observed between responders versus nonresponders.

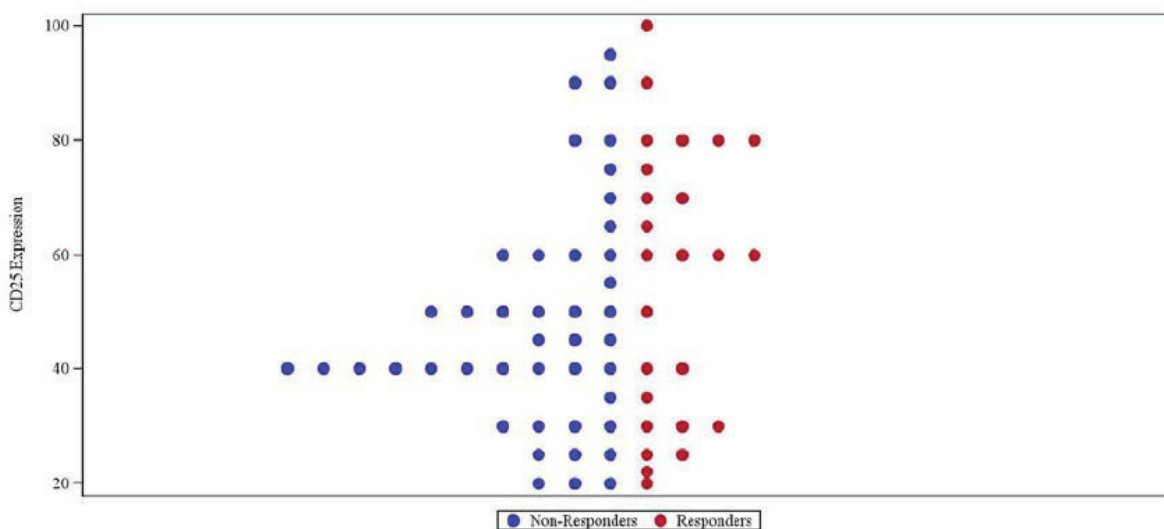
The Applicant's Position:

The results of additional analyses of efficacy in Study 302 were consistent with the results of analyses of the primary and secondary efficacy endpoints.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment. Regarding response rate based on CD25 expression, the FDA is providing additional information. An exploratory analysis was carried out regarding CD25 expression level and the efficacy outcome ORR. The distribution of CD25 expression for responders versus nonresponders is shown in the scatterplot below and demonstrates that no major differences in CD25 expression level are observed between the 2 groups.

Figure 8: Scatterplot for CD25 Expression by Subjects with or without Objective Response^a



^a Source: Clinical Summary Report for Study 302

The table below highlights that tumor response does not correlate with level of CD25 expression.

Figure 9: Tumor Response by CD25 Expression^a

	E7777 9 µg/kg CD25 Expression ^a		
	≥20% - <40% (N=19)	≥40% - <60% (N=23)	≥60% (N=26)
Best overall response from GRS, n (%)			
Complete response (CR)	2 (10.5)	0 (0.0)	4 (15.4)
Partial response (PR)	6 (31.6)	3 (13.0)	10 (38.5)
Stable disease (SD)	9 (47.4)	17 (73.9)	10 (38.5)
Progressive disease (PD)	2 (10.5)	0 (0.0)	1 (3.8)
Unknown	0 (0.0)	3 (13.0)	1 (3.8)
Objective response rate (CR + PR), n (%)	8 (42.1)	3 (13.0)	14 (53.8)
95% CI ^b	(20.3, 66.5)	(2.8, 33.6)	(33.4, 73.4)

^a Source: Clinical Summary Report for Study 302

8.1.3. Supportive Study E7777-J081-205

Trial Design

The Applicant's Description:

Study E7777-J081-205 (Study 205) was a multicenter, open-label, Phase 2 study in Japanese subjects with relapsed or refractory PTCL and CTCL (histopathologically diagnosed), that was the basis for approval of E7777 in Japan, in relapsed or refractory PTCL and CTCL. Study 205 evaluated the efficacy, safety, PK and immunogenicity of E7777. A total of 37 subjects (19 CTCL, 17 PTCL, and 1 other type of lymphoma) received E7777 9 µg/kg/day IV infusion (60 ±10 minutes) from Day 1 to Day 5 of each 21-day cycle up to a maximum of 8 cycles.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment and notes that Study 205 is considered supportive information.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint was ORR (BOR of CR or PR) assessed by an independent Efficacy

and Safety Evaluation Committee (ESEC). In order to evaluate both CTCL and PTCL subjects using the same set of criteria, BOR and ORR were evaluated by the IRC using the Overall T-Cell Lymphoma Response Criteria, which was developed using a combination of the criteria in Cheson, et al., 2007 and Olsen, et al., 2011. In CTCL subjects, ORR was also assessed by IRC using Olsen, et al., 2011 criteria. Secondary efficacy endpoints included PFS, DOR, TTR, CR rate and overall survival (OS).

Secondary endpoints included safety assessments (AEs, clinical laboratory parameters, vital signs, weight, ECOG, ECGs, ophthalmologic tests), PK and immunogenicity of E7777. Exploratory endpoints included evaluation of biomarkers in tumors and in blood (rate of CD25-positive cells in tumors; serum soluble IL-2 receptor (sIL-2R); lactate dehydrogenase (LDH) levels; T-cell subsets in peripheral blood).

The FDA's Assessment:

The FDA concurs with the Applicant's assessment and notes that Study 205 is considered supportive information.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Sample size: The sample size of approximately 35 subjects was estimated to provide a statistical power of 90% to detect a lower limit of the 95% CI exceeding the 5% threshold for an expected ORR of 25%. Six or more subjects with CTCL were targeted to evaluate the safety as a specific disease.

Analysis Populations:

- Full Analysis Set: All subjects who received at least 1 dose of study drug. Efficacy was evaluated using this set.
- Safety Analysis Set: All subjects who received at least 1 dose of study drug and had at least 1 evaluable post-baseline safety data. Safety was evaluated using this set.
- PK Analysis Set: All subjects who received at least 1 dose of study drug and had at least 1 evaluable serum concentration data.
- PD Analysis Set: All subjects is the group of subjects who received at least 1 dose of study drug and had at least 1 each of evaluable pre- and post-baseline PD data.

Primary Efficacy Endpoint Analysis: The ORR with the 2-sided exact 95% CI was calculated.

Secondary Efficacy Endpoint Analysis: PFS, DOR, TTR and OS were analyzed by the KM method (median with 95% CIs). The CR rate with the 2-sided exact 95% CI was calculated.

Safety Analysis: Safety data were summarized using descriptive statistics (e.g., n, mean, StDev, median, Q1, Q3, Min and Max for continuous variables; number and percentage for categorical variables). Safety data included AEs, clinical laboratory results, vital signs, and ECGs.

PK Analysis: E7777 serum concentrations for non-compartmental analysis were summarized using summary statistics (n, mean, StDev, median, Min and Max) by nominal time point.

PD analysis: Frequency and percentage of CD25-positive cells rate were calculated for each disease (PTCL, CTCL) and overall. Values (and change from baseline, if appropriate) of sIL-2R, LDH and T-cell subsets for each evaluation period were summarized using the number of subjects, mean, StDev, median, Min and Max for each disease and overall.

Immunogenicity Analysis: Anti-E7777/anti-IL-2 antibodies results and neutralizing anti-E7777/IL-2 antibodies results (positive/negative) were summarized by number of subjects and percentage by visit. Titer levels were summarized using summary statistics (n, mean, StDev, median, min and max) by visit.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment and notes that Study 205 is considered supportive information.

Protocol Amendments

The Applicant's Description:

The Study 205 protocol was amended 3 times (Table 11).

Table 11: Study E7777-J081-205 Protocol Amendments

Amendment (date)	Significant Changes to the Protocol
Amendment 01 (19 Feb 2016)	Preparation and Administration of the Study Drug was revised since it was confirmed that the study drug was stable within 24 hours after dispensing and 50-fold dilution of the study drug was not adsorbed to the infusion bag and infusion line.
Amendment 02 (07 Feb 2018)	Serum albumin concentrations inclusion criterion was revised from ≥ 3.0 g/dL to ≥ 3.5 g/dL. An exclusion criterion “Had complications or histories of polymyositis, dermatomyositis, mitochondrial myopathy, hyperthermia malignant and their relative disease” was added. To resume the administration of E7777, recovery of hypoalbuminaemia to $\leq$ Grade 1 (previously $\leq$ Grade 2). Management of capillary leak syndrome and of rhabdomyolysis were defined in the protocol. CPK was added to clinical laboratory tests. Weight measurements on Day 8 and Day 15 in each cycle and the last observation were added.
Amendment 03 (06 Aug 2018)	In an inclusion criterion, an exception for previous systemic chemotherapy was replaced from retinoid to etretinate, to consider a newly approved retinoid anticancer drug (bexarotene).

The FDA’s Assessment:

The FDA concurs with the Applicant’s Assessment.

8.1.4. Study Results for Supportive Study E7777-J081-205

Study E7777-J081-205 enrolled both CTCL and PTCL subjects, but the results described in this section will focus primarily on CTCL subjects, because CTCL is the target population for this BLA submission.

Compliance with Good Clinical Practices

Data and The Applicant’s Position:

Study 205 was performed in full compliance with ICH and all applicable local GCP and regulations. All required study documentation is archived as required by regulatory authorities.

The FDA’s Assessment:

The FDA concurs with the Applicant’s assessment.

Financial Disclosure

Data:

Eight clinical investigators in Study 205 had significant disclosable financial arrangements in the

form of honorarium and research donations (i.e., >\$25,0000). A list of investigators can be found in Module 1.3.4 Financial Certification and Disclosure documents. Details of financial disclosure are presented in Section 19.2.

The Applicant's Position:

As the sponsor of Study 205, Eisai has adequately disclosed any financial interests or arrangements with clinical investigators in accordance with the guidance for industry.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Patient Disposition

Data:

Forty-five subjects were screened for entry into the study; of these, 8 (17.8%) were screen failures and 37 (82.2%) were confirmed to be eligible. All 37 enrolled subjects received E7777 (17 PTCL, 19 CTCL, and 1 other type of lymphoma). Of the 19 CTCL subjects, 7 (36.8%) completed all study treatment (i.e., 8 cycles) and 12 (63.2%) discontinued study treatment before 8 cycles; the most common reasons were disease progression and AEs (3 subjects each), and subject choice (2 subjects). The 17 PTCL and 1 other type of lymphoma subjects all discontinued study treatment before completion of 8 cycles .

The Applicant's Position:

The disposition of CTCL subjects within Study 205 demonstrates reasonable retention in the study to demonstrate efficacy and safety of treatment. The number of subjects enrolled was consistent with the planned sample size.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Protocol Violations/Deviations

Data:

Minor deviations from the protocol were reported for 27 subjects (73.0%). No subjects received the incorrect treatment. No major protocol deviations per protocol or related to COVID-19 were reported.

The Applicant's Position:

Study 205 was effectively monitored to minimize protocol violations and deviations.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Table of Demographic Characteristics

Data:

Table 12: Demographic Characteristics of Subjects: Study E7777-J081-205

Category	PTCL (N=17)	CTCL (N=19)	Overall (N=36)
Age (years) ^a			
Mean (Standard deviation)	66.7 (9.16)	55.3 (15.09)	60.7 (13.73)
Median	66.0	52.0	64.5
Minimum, Maximum	49, 82	27, 81	27, 82
Age group, n (%)			
<65 years	6 (35.3)	12 (63.2)	18 (50.0)
≥65 years	11 (64.7)	7 (36.8)	18 (50.0)
Sex, n (%)			
Male	12 (70.6)	13 (68.4)	25 (69.4)
Female	5 (29.4)	6 (31.6)	11 (30.6)
Race, n (%)			
Japanese	17 (100.0)	19 (100.0)	36 (100.0)
ECOG Performance Status, n (%)			
0	10 (58.8)	13 (68.4)	23 (63.9)
1	7 (41.2)	6 (31.6)	13 (36.1)

Percentages are based on the number of subjects in the relevant group.

ECOG = Eastern Cooperative Oncology Group.

a: Age is calculated at date of informed consent.

The Applicant's Position:

Demographic characteristics of subjects in Study 205 were consistent with the target population of patients with relapsed or refractory CTCL and PTCL in Japan.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Disease stage of CTCL diagnosed by investigator (Olsen, et al., 2007) was IA in 2 subjects (10.5%), IIB in 11 subjects (57.9%), and IIIA, IVA, and IVB in 2 subjects each (10.5%). Median number of prior systemic chemotherapy regimen was 1.0 (range: 1 to 6) in CTCL subjects; all subjects had previously received systemic anticancer therapy. Among 19 CTCL subjects, 18 (94.7%) had received topical therapy, 15 (78.9%) had received extracorporeal therapy (except radiotherapy), 12 (63.2%) had received systemic anti-neoplastic therapy (except systemic cytotoxic chemotherapy), 9 (47.4%) had received radiotherapy, and 3 (15.8%) had received surgery.

The Applicant's Position:

Disease characteristics and prior therapy of subjects in Study 205 were consistent with the target population of patients with relapsed or refractory CTCL and PTCL in Japan.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

There was no significant noncompliance with the treatment regimen. Subjects with CTCL received a median of 5.0 cycles (range: 1 to 8), and 11 subjects (57.9%) received 5 or more cycles. Median relative dose intensity for CTCL subjects was 85.3%. Concomitant medications were provided as Listings in the study report, and there were no protocol-defined rescue medications.

The Applicant's Position:

There were no concerns relating to study drug compliance.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

For the primary efficacy endpoint of ORR assessed by the ESEC (based on Overall T-Cell Lymphoma Response Criteria), among 19 subjects with CTCL, none achieved a CR, 6 subjects (31.6%) achieved PR, and the ORR was 31.6% (95% CI: 12.6%, 56.6%).

The ORR by IRC based on GRS of CTCL subjects using Olsen, et al., 2011 criteria was 36.8% (95% CI: 16.3%, 61.6%) with no subjects achieving a CR and 7 subjects achieving a PR.

The Applicant's Position:

The ORR results in Study 205 were consistent with the results of Study 302.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Data Quality and Integrity

Data:

Quality and integrity of study data were assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in the Study 205 protocol.

The Applicant's Position:

There are no concerns relating to data quality and integrity.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Efficacy Results – Secondary and other relevant endpoints

Data:

In CTCL subjects, median DOR was 4.83 months (95% CI: 2.66, NE), median TTR was 2.12 months (range: 1.0 to 4.6), and median PFS was 4.2 months.

There was no requirement for demonstrating CD25 expression for enrollment, but the level of CD25 expression was determined retrospectively. Association analysis between CD25 expression level and the drug response suggests there is no statistically significant association between CD25 expression level and responder status in subjects with CTCL in Study 205 (Fisher exact test).

Subgroup analyses for CTCL subjects conducted by sex, age group, ECOG, CCR4 status, CD25-positive cell rate, relapsed/refractory disease, prior number of systemic chemotherapy regimen, and prior use of newly approved agents showed no notable differences in efficacy by any category except sex, where a response was reported for 6 of 13 males (ORR 46.2%; 95% CI: 19.2, 74.9) and for 0 of 6 females (ORR 0.0%; 95% CI: 0.0, 45.9).

The Applicant's Position:

The secondary and exploratory efficacy results in Study 205 support the efficacy of E7777 in subjects with CTCL reported for Study 302. There was no association between CD25 expression level and responder status among CTCL subjects.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Dose/Dose Response

Data and The Applicant's Position:

Not applicable. Study 205 was a single dose study

The FDA's Assessment:

The FDA concurs with the Applicant's assessment. Regarding FDA's review of the recommended dose, see Section 6.2.2.

Durability of Response

Data:

In CTCL subjects, median DOR was 4.83 (95% CI: 2.66, NE) months.

The Applicant's Position:

Durable responses to E7777 treatment were observed.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment and notes that Study 205 is considered supportive information.

Persistence of Effect

Data and The Applicant's Position:

Not applicable. No persistence of effect data from Study 205 are submitted with this BLA.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data and The Applicant's Position:

Not applicable. Patient-reported outcomes were not evaluated in Study 205.

The FDA's Assessment:

Not applicable

Additional Analyses Conducted on the Individual Trial

Data and The Applicant's Position:

Not applicable. No additional analyses were conducted on this trial.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

8.1.5. Supportive Study E7777-J081-101

Trial Design

The Applicant's Description:

Study E7777-J081-101 (Study 101) was a multicenter, open-label, dose-escalation, Phase 1/1b study in Japanese subjects with relapsed or refractory PTCL and CTCL to evaluate the safety and tolerability of E7777 monotherapy. E7777 dose was escalated stepwise to determine the MTD.

A total of 13 subjects received E7777 (6, 9, or 12 µg/kg) administered by IV infusion over 60 ± 10 minutes daily from Day 1 to Day 5 of each 21-day cycle up to a maximum of 8 cycles.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment and notes that Study 101 is considered supportive information.

Study Endpoints

The Applicant's Description:

Safety endpoints: AEs, SAEs, laboratory parameters, vital signs, weight, ECOG, ECGs, physical examinations, ophthalmologic examinations.

Efficacy endpoints were exploratory: BOR, complete response rate (CRR), ORR, and disease control rate (DCR). Efficacy data from Study 101 are not included in the BLA. Other endpoints: PK, immunogenicity, sIL-2R, CD25 expression.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Sample size: The sample size of approximately 24 subjects was based on up to 6 subjects receiving 1 of up to 4 dose levels to determine the MTD.

Analysis Populations:

- Safety Analysis Set: all subjects who received at least one dose of the study drug with at least one evaluable, post-baseline safety datum.
- Efficacy Analysis Set: all subjects who received at least one dose of the study drug with at least one evaluable, post-baseline efficacy datum.
- PK Analysis Set: all subjects in whom at least one PK parameter could be calculated.
- PD Analysis Set: all subjects who had sIL-2R data at least for one time point.

Efficacy Analyses: BOR summarized by dose group, disease diagnosis, and overall. CRR, ORR, and DCR were provided with corresponding exact 95% CI by dose group and overall.

Safety Analysis: The number and the percentage of subjects developing TEAEs were calculated by dose group and overall. For other safety parameters, continuous variables were summarized as recorded values and changes from baseline at each scheduled visit by dose group and overall; categorical variables were presented as numbers and percentages of subjects in each category at each scheduled visit by dose group and overall. For criteria defined by National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE), the number and percentage of subjects with each grade were presented by visit by dose group and overall.

PK Analysis: E7777 serum concentrations for non-compartmental analysis were summarized by nominal time point. Dose-proportionality was investigated using exposure parameters obtained from non-compartmental analysis.

PD analysis: Recorded values and change from baseline for sIL-2R were summarized for each scheduled visit by dose group and overall using descriptive statistics. CD25 expression was summarized.

Immunogenicity Analysis: The number of subjects with at least one positive result was provided for the anti-E7777 antibody and the anti-IL-2 antibody.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment and notes that Study 101 is considered supportive information.

Protocol Amendments

The Applicant's Description:

The original Study 101 protocol (version 1; 16 Jun 2011) was amended 12 times to the final protocol (version 13; 08 Apr 2015; Table 13). Protocol versions 2 and 3 were not used; version 4 (amendment 03) was similar to version 1, the only major change was the addition of the sponsor details. Amendments 06 (14 Feb 2012), 08 (04 Apr 2013), 11 (20 May 2014), and 12 (08 Apr 2015) were primarily administrative.

Table 13: Study E7777-J081-101 Protocol Amendments

Amendment (date)	Significant Changes to the Protocol
Amendment 04 (11 Nov 2011)	Reporting of significant laboratory abnormality was removed from the protocol, as this could be obtained through regular appropriate monitoring. Ocular injury was included as an AE specific to the study and requiring follow up.
Amendment 05 (20 Dec 2011)	Criteria for DLTs, dose interruption and dose reduction were modified. Preventive use of medications to reduce toxicities of E7777 in Cycle 1 was implemented, and those for AEs which occurred in Cycle 1 were allowed for subsequent cycles.
Amendment 07 (18 Sep 2012)	Grade 3 transient abnormal clinical laboratory values without clinical symptoms were added as an exception of the DLT criteria and included in the criteria for dose reduction. The exception to allow inclusion of subjects with hepatic infiltration, AST and ALT $\leq 5.0 \times$ ULN was removed, i.e., only subjects with AST and ALT $\leq 3.0 \times$ ULN became eligible, and was also deleted from the criteria for initiating the next treatment cycle. Cholinesterase was added as a laboratory parameter. Measurements of serum albumin on Cycle 1 Days 1 to 5 (and also Days 2 to 5 in subsequent cycles, if needed) before E7777 administration were added on the schedule of assessments.
Amendment 09 (19 Aug 2013)	The exclusion criterion for duration since the last administration of study drug in another clinical study was changed from "3 month" to "4 weeks (3 months for antibody drug)".
Amendment 10 (20 Nov 2013)	The sponsor decided not to conduct the Phase 1b part of the study

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

8.1.6. Study Results for Supportive Study E7777-J081-101

This is a supportive study, but since it was a dose escalation study, and only 2 CTCL subjects were enrolled and received the E7777 9 µg/kg dose, the emphasis of the data presented is on safety rather than efficacy.

Compliance with Good Clinical Practices

Data and The Applicant's Position:

Study 101 was performed in full compliance with ICH and all applicable local GCP and regulations. All required study documentation is archived as required by regulatory authorities.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Financial Disclosure

Data and The Applicant's Position:

Not applicable. No financial disclosures for Study 101 are submitted with this BLA

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Patient Disposition

Data:

Thirteen (13) subjects enrolled in the study and received E7777 at 6 µg/kg/day (N=3), 9 µg/kg/day (N=7) and 12 µg/kg/day (N=3). Of the 13 treated subjects, 12 were DLT evaluable. One (1) subject in the 9 µg/kg/day group completed the entire study (i.e., 8 cycles) and 12 discontinued the study due to disease progression, subject choice (4 subjects each; 30.8%), AE (3 subjects; 23.1%), or investigator's decision (1 subject; 7.7%) as the primary reason for discontinuation.

The Applicant's Position:

The disposition of subjects within Study 101 demonstrates adequate assessment of safety to determine the MTD of E7777 in the study population.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Protocol Violations/Deviations

Data:

Minor deviations from the protocol were reported for 8 subjects (61.5%). No subjects received the incorrect treatment. No major protocol deviations per protocol or related to COVID-19 were reported

The Applicant's Position:

Study 101 was effectively monitored to minimize protocol violations and deviations.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Table of Demographic Characteristics

Data:

Table 14: Demographic Characteristics of Subjects: Study E7777-J081-101

Category	6 µg/kg/day (N=3)	9 µg/kg/day (N=7)	12 µg/kg/day (N=3)	Total (N=13)
Age ^a (years)				
Mean (Standard deviation)	69.7 (5.51)	49.9 (17.74)	66.3 (4.16)	58.2 (15.98)
Median	70.0	44.0	65.0	64.0
Minimum, Maximum	64, 75	23, 75	63, 71	23, 75
Sex, n (%)				
Male	2 (66.7)	4 (57.1)	2 (66.7)	8 (61.5)
Female	1 (33.3)	3 (42.9)	1 (33.3)	5 (38.5)
Race, n (%)				
Japanese	3 (100.0)	7 (100.0)	3 (100.0)	13 (100.0)
ECOG Performance Status, n (%)				
0	3 (100.0)	6 (85.7)	2 (66.7)	11 (84.6)
1	0	1 (14.3)	1 (33.3)	2 (15.4)
Disease Diagnosis, n (%)				
PTCL	3 (100.0)	5 (71.4)	2 (66.7)	10 (76.9)
CTCL	0	2 (28.6)	1 (33.3)	3 (23.1)

Percentages are based on the total number of subjects in the relevant treatment group.

CTCL = cutaneous T-cell lymphoma, ECOG = Eastern Cooperative Oncology Group, PTCL = peripheral T-cell lymphoma.

a: Age is calculated at date of informed consent.

The Applicant's Position:

Demographic characteristics of subjects in Study 101 were consistent with the target population of patients with relapsed or refractory CTCL and PTCL in Japan.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

At diagnosis, PTCL disease stages (10 subjects) were 1 at Stage I, 2 at Stage II, 3 at Stage III, and 4 at Stage IV; all 3 CTCL subjects had MF, with 1 subject each at Stage IIA, IIB, and IVA. Twelve subjects (92.3%) had previously received anticancer chemotherapy. One subject (7.7%) had received previous anticancer surgical therapy, 3 subjects (23.1%) had received previous anticancer radiotherapy, and 4 subjects (30.8%) had received other previous anticancer therapy including NB-UVB phototherapy, PUVA photochemotherapy, and interferon.

The Applicant's Position:

Disease characteristics and prior therapy of subjects in Study 101 were consistent with the target population of patients with relapsed or refractory CTCL and PTCL in Japan

The FDA's Assessment:

The FDA concurs with the Applicant's assessment and notes that Study 101 is considered supportive information.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

There was no significant noncompliance with the treatment regimen. In Cycle 1, the median number of doses received was 5.0 (range: 4.0, 5.0) and the mean was 4.9. Concomitant medications were provided as Listings in the study report. The use of rescue medication was not planned in the study.

The Applicant's Position:

There were no concerns relating to study drug compliance.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Efficacy was an exploratory endpoint. Two subjects with CTCL received E7777 9 µg/kg; both had a BOR of SD.

The Applicant's Position:

Evaluation of efficacy in Study 101 was exploratory.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment and notes that Study 101 is considered supportive information.

Data Quality and Integrity

Data:

Quality and integrity of study data were assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in the Study 101 protocol.

The Applicant's Position:

There are no concerns relating to data quality and integrity.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Efficacy Results – Secondary and other relevant endpoints

Data and The Applicant's Position:

Not applicable. Preliminary antitumor activity was an exploratory endpoint; there are no secondary efficacy data to report.

The FDA's Assessment:

Not applicable.

Dose/Dose Response

Data and The Applicant's Position:

Not applicable. No dose response analysis was planned or conducted in Study 101.

The FDA's Assessment:

Not applicable.

Durability of Response

Data and The Applicant's Position:

Not applicable. There was no analysis of DOR in Study 101.

The FDA's Assessment:

Not applicable.

Persistence of Effect

Data and The Applicant's Position:

Not applicable. There was no persistence of effect analysis in Study 101.

The FDA's Assessment:

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable. No PRO data were collected in Study 101.

The FDA's Assessment:

Not applicable.

Additional Analyses Conducted on the Individual Trial

Data and The Applicant's Position:

Not applicable. No additional analyses were conducted on data from Study 101.

The FDA's Assessment:

Not applicable.

8.1.7. Integrated Review of Effectiveness

The FDA's Assessment:

An integrated assessment of effectiveness was not conducted. Each trial, Study 302 (pivotal study), Study 202 (supportive), and Study 101 (supportive), were evaluated

separately regarding efficacy.

8.1.8. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Efficacy Across E7777 Trials

The results from the pivotal Study E7777-G000-302 are intended to be the basis for full approval of a Biologics License Application (BLA) for E7777. Efficacy is assessed across 1 other E7777 study: Study 205, conducted in Japan, that was the basis for approval of E7777 in Japan. Note that comparison of efficacy across trials does not include the supportive Study 101, which only had 2 CTCL subjects that received E7777 at the 9 µg/kg dose.

The primary efficacy endpoint in Study 302 was ORR based on GRS per Olsen, et al., 2011 criteria as assessed by IRC. There were 25 responders out of 69 subjects in the Primary Efficacy Analysis Set as assessed by the IRC, giving an ORR of 36.2% (95% CI: 25.0%, 48.7%). Similar response rates were seen whether evaluated by investigator assessment (42.3% [95% CI: 30.6%, 54.6%] in the Investigator Stage I to III Efficacy Analysis Set or per IRC using the method of Prince (2010) (36.2% [25.0%, 48.7%] in the Primary Efficacy Analysis Set.

The ORR of CTCL subjects in Study 205 assessed by IRC using either Olsen (2011) criteria or the Overall T Cell Lymphoma Response Criteria was consistent as well at 36.8% (CI: 16.3, 61.6) and 31.6% (CI: 12.6, 56.6), respectively.

Efficacy Across E7777 and ONTAK Trials

The historical reference ONTAK study, Study 93-04-11/L4389-11 (hereafter referred to as Study 11), served as the basis for the full approval of the ONTAK (BLA 103767). As E7777 is intended to replace ONTAK, the results of E7777 are also discussed, but separately, with reference to efficacy data from ONTAK.

ONTAK Study 11 was a randomized, placebo-controlled Phase 3 study of ONTAK in subjects with Stage IA-III persistent or recurrent CTCL. Subjects were randomized to ONTAK 9 µg/kg (N=45), 18 µg/kg (N=55) or placebo (N=44).

The primary efficacy endpoint results were similar between E7777 Study 302 and ONTAK Study 11. ORR using the criteria in Olsen (2011) was 36.2% for E7777 in Study 302 by IRC and 42.3% by investigator assessment. For ONTAK Study 11, ORR using the criteria in Prince (2010) was in the same range (37.8% and 49.1% for the 9 µg/kg and 18 µg/kg dose groups, respectively).

For both E7777 Study 302 and ONTAK Study 11, objective responses were observed in all disease stages from Stage I to III.

The Applicant's Position:

Across Studies 302 and 205, the efficacy results for E7777 were similar overall. The primary efficacy endpoint, ORR, for both studies were 36.2% in Study 302 and 36.8% in Study 205. The efficacy results of E7777 were also, in general, similar to efficacy reported for ONTAK in the historical reference Study 11. The primary efficacy endpoint, ORR, was in a similar range: 36.2% in E7777 Study 302, and 37.8% and 49.1% for ONTAK at 9 µg/kg and 18 µg/kg, respectively. Overall, the similarity in ORR for E7777 and ONTAK was observed despite a more heavily pre-treated population in the E7777 studies and despite the changes in the treatment of CTCL (e.g., FDA approval of new targeted agents) since the ONTAK Study 11 was conducted approximately 15 years earlier.

Taken together, the efficacy results across trials show that treatment of CTCL subjects with E7777 results in a meaningful clinical benefit, and that E7777 has a similar efficacy profile when compared across studies and when compared with historical ONTAK efficacy results.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Secondary and Other Endpoints

Data:

The secondary/other endpoint assessments are across the same E7777 Studies 302 and 205, as for the primary endpoint. Secondary/other endpoint assessments are also presented for ONTAK Study 11 as a historical reference.

E7777 Studies

Duration of response

DOR for E7777 was in a similar range for both Studies 302 and 205. Among the 25 subjects in the Study 302 Primary Efficacy Analysis Set who were responders, the median (95% CI) DOR using KM estimates was NE, but a median observed DOR of 6.47 months was reported. In the Study 205 Full Analysis Set (FAS), among the 6 CTCL subjects who were responders (based on the Overall T-Cell Lymphoma Response Criteria [Study 205]), the median DOR was 4.83 (2.66, NE) months.

Time to response

Time to response was similarly rapid in both Studies 302 and 205. In the Study 302 efficacy analysis sets, the majority of responders achieved responses after 1 to 2 cycles of treatment (68% and 70% in the Primary Efficacy Analysis Set and Investigator Stage I to III Efficacy Analysis Set, respectively). The median TTR was 1.41 months by both IRC and investigator assessments. Median TTR in the Study 205 FAS, was similar at 2.12 months (range: 1.0 to 4.6).

Skin response

Skin response characteristics were similar in both Study 302 and 205 with a high proportion of subjects achieving a reduction in skin tumor burden. The majority of subjects in Study 302 who had both baseline and postbaseline mSWAT scores had reductions from baseline to postbaseline nadir (84.4%; 54/64), with 48.4% of subjects (31 of 64) with a $\geq 50\%$ reduction, 25.0% of subjects (16 of 64) with a $>90\%$ reduction, and 12.5% of subjects (8 of 64) with a 100% reduction by IRC. Similarly, of the 17 CTCL subjects in Study 205 who had both baseline and postbaseline mSWAT score data by investigator's assessment, 14 subjects (82.4%) experienced a decrease of their mSWAT scores from baseline, and, of these, 8 CTCL subjects (47.1%) experienced more than a 50% reduction in their mSWAT scores from baseline.

Other

- In Study 302, BOR (IRC, Olsen 2011) was PR in 19 subjects (27.5%) and CR in 6 subjects (8.7%). In the Study 205 FAS, none achieved a CR and 7 subjects (36.8%) had a BOR of PR.
- In Study 302, median PFS was NE in the Primary Efficacy Analysis Set. In the Study 205 FAS, the median PFS for CTCL subjects was 4.24 months (95% CI: 2.56, NE).
- In Studies 302 and 205 CTCL subjects, no major difference in CD25 expression level was observed between responders and nonresponders.

E7777 and ONTAK Trials

The DOR for E7777 Study 302 and ONTAK Study 11, although using slightly different tumor assessment methods, were in the same range as well. The median observed DOR for E7777 in Study 302 was 6.47 months and for ONTAK Study 11, the KM estimate of DOR in the 2 ONTAK dose groups combined was 7.75 months. The TTR was similar for E7777 Study 302 and ONTAK Study 11; median TTR was 1.4 months for both, with most responses occurring after receiving 1 to 2 cycles of treatment.

The Applicant's Position:

Major secondary endpoint results were in general similar for E7777 in Studies 302 and 205, as well as similar between E7777 in Study 302 and ONTAK in Study 11.

DOR was in a similar range for both Studies 302 and 205 (observed median of 6.47 months for Study 302 versus KM median of 4.83 months for Study 205), and in both studies the TTR was similar (median 1.41 months versus 2.12 months for Study 302 versus Study 205, respectively).

These similarities were observed despite some differences in patient population (in CTCL disease stage, prior anticancer therapy and CD25 expression in tumor) and in some tumor assessment methodologies.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment.

Subpopulations

Data:

Given the small numbers of subjects in Study 302 (Primary Efficacy Analysis Set, N=69) and especially in Study 205 (N=19 CTCL subjects), comparison of efficacy within subgroups between the 2 studies is not meaningful. Furthermore, Studies 302 and 205 analyzed different categories of subgroups, making it impractical to make many specific cross-study subpopulation comparisons.

There was no notable difference between the <65 and ≥65 age categories for any tumor response variable for either study. It is, however, worth noting that since the ORR for both studies were very similar, and there is one major demographic difference between the studies, i.e., race, it could be surmised that efficacy is not largely different in white/black versus in Japanese populations.

The Applicant's Position:

Given the small number of subjects, particularly in Study 205, and the differences in subgroup categories, comparison of efficacy within subgroups across studies is not meaningful.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment that the limited sample size precludes any meaningful interpretation of the subgroup results.

8.1.9. Integrated Assessment of Effectiveness

Data:

Efficacy data were not integrated across studies. Assessment of efficacy across individual studies is described in Section 8.1.8.

The Applicant's Position:

Efficacy data were not integrated across studies. Assessment of efficacy across individual studies is described in Section 8.1.8.

The FDA's Assessment:

An integrated assessment of effectiveness was not conducted. Each trial, Study 302 (pivotal study), Study 202 (supportive), and Study 101 (supportive), were evaluated separately regarding efficacy.

The efficacy of denileukin diftitox is primarily based on IRC-assessed ORR in Study 302, a single-arm trial that enrolled patients with relapsed or refractory CTCL after at least 1 prior line of systemic therapy. Sixty-nine patients with Stage I-III CTCL who previously received 1 prior systemic therapy and received denileukin diftitox at the recommended dosage were evaluable for efficacy. In the efficacy population, all patients had at least 1 prior systemic therapy and the median number of prior therapies was 4 (range: 1-18). By IRC assessment, the ORR was 36.2% (95% CI: 25.0, 48.7) and the complete remission and partial response rates were 9% and 27% respectively, according to the Olsen (2011) criteria, with a median time to response of 1.4 months. Out of the 25 respondents, none experienced an event of progression or death. The median duration of response using Kaplan-Meier estimate could not be determined as all responders were censored. In patients who achieved a response, the duration of response exceeded 6 months in 52% (13/25) and 12 months in 20% (5/25).

While the data related to durability of response are limited by the degree of censoring, the ORR supports the determination that denileukin diftitox has clinically meaningful activity in patients with relapsed or refractory Stage I-III CTCL.

(b) (4)

8.2 Review of Safety

8.2.1 Safety Review Approach

Data:

This safety review consists of safety data from the Phase 3 Study 302, with supportive data from Studies 205 and 101. The primary focus is on the Phase I-III Safety Set from Study 302,

because it is identical to the Primary Efficacy Analysis Set. Safety data from these 3 studies was pooled and divided into 4 subgroups as presented in the Summary of Clinical Safety. The safety profile of E7777 is also discussed relative to that of ONTAK from Study 11, which is considered a historical reference.

All safety data were from subjects that received E7777 9 µg/kg administered by IV infusion over 60 minutes on 5 consecutive days every 21-day cycle.

The study design of each individual E7777 Clinical Study was reviewed in Section 8.1.

- Study 302 was a Phase 3 single-arm, open label study conducted in the United States and Australia in subjects with persistent or recurrent CTCL. A total of 69 subjects with Stage I-III CTCL received E7777 9 µg/kg. An additional 29 subjects had Stage IV CTCL, resulting in a total of 98 subjects with Stage I-IV CTCL that received E7777 9 µg/kg.
- Study 205 was a Phase 2 single-arm, open label study conducted in Japan in CTCL (n=19) and PTCL (n=17), and 1 subject with another type of lymphoma, that was the basis for approval of E7777 in Japan (N=37); all subjects received E7777 9 µg/kg
- Study 101 was a Phase 1 single-arm, open label study conducted in Japan in subjects with relapsed or refractory PTCL (N=5) or CTCL (N=2); total N=7 who received E7777 9 µg/kg.

ONTAK Study 11 was a randomized, placebo-controlled Phase 3 study of ONTAK in subjects with CTCL. Subjects were randomized to ONTAK 9 µg/kg (N=45), 18 µg/kg (N=55) or placebo (N=44). Safety data from ONTAK Study 11 is pooled from the 9 µg/kg and 18 µg/kg dose groups (total N=100), unless otherwise specified. ONTAK safety data were not included in the E7777 pooled safety datasets.

Safety data are presented for 4 E7777 safety analysis sets (Table 15):

Safety Set	Study 302 Stage I-III	Study 302 Stage I-IV	All Study/All Stage CTCL	All CTCL/PTCL
Total Number of Subjects ^a	69	98	119	142
Source Study (number of subjects)	Study 302 (69)	Study 302 (98)	Study 302 (98) Study 205 (19) Study 101 (2)	Study 302 (98) Study 205 (37) Study 101 (7)
Description	All subjects with Stage I-III CTCL in Study 302	All subjects with any stage CTCL in Study 302	All subjects with any stage CTCL in Study 302, Study 205, and Study 101	All subjects with CTCL, PTCL, or other type of lymphoma in Study 302, Study 205, and Study 101

CTCL = cutaneous T-cell lymphoma, PTCL = peripheral T-cell lymphoma
a: All subjects received E7777 9 µg/kg.

Safety was assessed based on established and accepted criteria: TEAEs, clinical laboratory results, vital sign measurements, physical exam findings, ECG findings, and concomitant medication use. AEs of special interest (AESI) for E7777 were predefined based on the ONTAK Study 11 safety profile. These were capillary leak syndrome (CLS), hepatotoxicity, visual impairment, infusion reactions, hypersensitivity, rash, infections, and thrombotic events.

The Applicant's Position:

The approach to the safety review of E7777 in this BLA is to focus primarily on the Study 302 Stage I-III Safety Set, which is identical to the Primary Efficacy Analysis Set. Pooling of E7777 safety data into 4 safety sets allows consideration of the possible effects of independently conducted studies in different study populations on the safety profile of E7777 at a dose of 9 µg/kg. The pooling strategy utilizes safety data from all subjects that received E7777 9 µg/kg in the E7777 clinical study program. Consideration of safety data from ONTAK Study 11 provides additional insight as a historical reference.

The FDA's Assessment:

The FDA's safety review was based on the Applicant's datasets for the primary safety population of 119 patients with relapsed or refractory CTCL treated with a dose of 9 µg/kg across three clinical studies (Studies 302, 205, 101) as outlined in the table above.

The FDA clinical review of safety for this BLA is also based on the following:

- Clinical Study Report for study E7777-G000-302
- Protocol and statistical analysis plan for study 302
- Case report forms and safety narratives
- Summary of clinical safety
- Proposed labeling for E7777

The Applicant reported adverse events using single MedDRA preferred terms (PTs). For increased sensitivity, FDA used a combination of grouped PTs, as defined in Appendix 19.5. Adverse events that involve more than one body system were consolidated and reported under the most commonly involved or most appropriate body system. Unless noted, all presented analyses use the FDA grouped PTs.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

A total of 142 subjects received treatment with E7777 9 µg/kg/day via IV infusion over 60 minutes daily from Day 1 through Day 5 of each 21-day cycle, for up to 8 cycles. In Study 302, treatment beyond 8 cycles was permitted if there was clinical benefit as assessed by the investigator. Table 15 summarizes the number of subjects, source study, and description of each of the 4 safety analysis sets. Duration of treatment was defined as the number of weeks the subject received treatment, including any dose interruptions days. The median duration of treatment in the Study 302 Stage I-III Safety Set was 15.71 weeks, the median cumulative number of cycles of E7777 was 6.0, with a median number of infusions per cycle of 4.88. Exposure to E7777 in the Study 302 Stage I-IV, All Study/All Stage CTCL, and All CTCL/PTCL Safety Sets was similar to that in the Study 302 Stage I-III Safety Set (Table 16).

Table 16: Summary of Administration of E7777				
Parameter Statistic	Study 302 Stage I-III (N=69)	Study 302 Stage I-IV (N=98)	All Study/ All Stage CTCL (N=119)	All CTCL/PTCL (N=142)
Cumulative Number of Cycles Received^a				
n	69	98	119	142
Mean (SD)	7.0 (6.25)	6.1 (5.63)	5.9 (5.25)	5.4 (5.00)
Median	6.0	4.0	5.0	4.0
Min, Max	1, 42	1, 42	1, 42	1, 42
Overall Number of Infusions				
n	69	98	119	142
Mean (SD)	33.1 (29.00)	28.7 (26.37)	27.9 (24.66)	25.6 (23.50)
Median	28.0	20.0	23.0	20.0
Min, Max	1, 189	1, 189	1, 189	1, 189
Overall Number of Infusions per Cycle				
n	69	98	119	142
Mean (SD)	4.58 (0.697)	4.56 (0.764)	4.61 (0.725)	4.65 (0.691)
Median	4.88	4.88	5.00	5.00
Min, Max	1, 5	1, 5	1, 5	1, 5
Duration of Treatment (weeks)^b				
n	69	98	119	142
Mean (SD)	20.31 (20.701)	17.25 (18.803)	16.73 (17.545)	15.11 (16.695)
Median	15.71	12.07	12.71	10.71
Min, Max	0.1, 126.1	0.1, 126.1	0.1, 126.1	0.1, 126.1

Percentages are based on the total number of subjects in the relevant safety set.

CTCL = cutaneous T-cell lymphoma, Max = maximum, Min = minimum, PTCL = peripheral T-cell lymphoma.

a: A subject is considered to have received 1 cycle if he/she received at least 1 dose on Day 1, 2, 3, 4 or 5 of a cycle.

b: Duration of treatment (weeks) = (date of last dose – date of first dose + 1) / 7..

The Applicant's Position:

Overall exposure to E7777 was similar across datasets.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The median exposure in the primary safety population was 5 cycles or 12.7 weeks. Of note, the median duration of treatment, cumulative number of cycles received, and overall number of infusions was higher in the Study 302 Stage I-III safety set compared to the 3 other safety sets. The reason for this difference may be due to the inclusion of only early-stage CTCL patients within the Study Stage I-III safety population as compared to the other 3 safety sets that included Stage IV CTCL patients. Nevertheless, the exposure data are limited beyond 6 cycles of treatment, providing limited safety data for longer-term exposure of E7777.

Relevant characteristics of the safety population:

Data:

Of the 69 subjects in the Study 302 Stage I-III Safety Set, the median age was 64.0 years, 65.2% were male, 72.5% were White, and 18.8% were Black or African American. Demographic characteristics of the Study 302 Stage I-III Safety set were consistent with those for the other 3 safety sets, except for Asian race. Note that the 2 Japanese studies contributing data to the All Study/All Stage CTCL and All CTCL/PTCL Safety Sets enrolled only Asian subjects, and had lower mean and median body weight relative to the 2 other safety sets.

Baseline disease characteristics were generally similar across the safety sets; most subjects in all 4 safety sets had the MF type of CTCL, with the highest proportion in the Study 302 Stage I-III Safety Set. The majority of subjects in all 4 safety sets had Stage IIB or higher CTCL, with the lowest proportion in the Study 302 Stage I-III Safety Set, because this set did not include subjects with Stage IV CTCL.

The Applicant's Position:

Overall, demographic and baseline disease characteristics of the safety populations were generally similar across the safety sets. Differences between the safety sets can be attributed to the differences in study subject populations and geographical locations of study sites.

The FDA's Assessment:

The FDA agrees with the Applicant's position. For the safety population of 119 patients, the median age was 64 (range: 23 to 87), 49% were 65 years of age or older, 63% were male, 61% were White, 19% were Asian, 13% were Black or African American, and 12% were Hispanic or Latino. The CTCL disease stage was IA in 6%, IB in 13%, IIA in 8%, IIB in 29%, IIIA in 8%, IIIB in 6%, IVA in 25%, and IVB in 3%.

Adequacy of the safety database:

Data:

The evaluation of safety is based on data from a total of 142 subjects treated with E7777 at the 9 µg/kg dose, and pooled from Studies 302, 205 and 101, using established and accepted methods of reporting safety-related information.

In addition, Eisai obtained regulatory approval of E7777 (Remitoro) in Japan in March, 2021 for patients with relapsed or refractory PTCL and CTCL. As of 17 Mar 2022, the estimated total number of patients exposed to Remitoro was (b) (4), including 43 subjects in the ongoing postmarketing, observational study E7777-M081-501 (NCT05137847).

The Applicant's Position:

The E7777 safety database includes clinical trial safety data from a total of 119 subjects with CTCL and 23 subjects with PTCL that received E7777 at the 9 µg/kg dose, and an additional (b) (4) patients with relapsed or refractory PTCL or CTCL in the postmarketing setting in Japan. Given that CTCL is a rare disease, the available safety dataset is sufficient to support an informed assessment of the safety profile of E7777 in patients with persistent or recurrent CTCL.

The FDA's Assessment:

The size of the integrated safety database with a primary safety population of 119 patients with CTCL treated at the recommended dose of 9 µg/kg is considered adequate for review.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

In Study 302, standard data review was consistently applied to all safety data, including TEAEs, SAEs, deaths, adverse events of special interest (AESI), TEAEs leading to dose modification or discontinuation of treatment. Narratives have been prepared for all SAEs, deaths, TEAEs leading to discontinuation, and all non-serious AESI events. Coding of AEs was done according to standard MedDRA methods. Company SOPs ensured that safety data was reviewed consistently across all studies.

The Applicant's Position:

The quality and integrity of the submitted datasets and individual case narratives are sufficiently complete to allow a reliable and thorough review of safety.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Categorization of Adverse Events

Data:

AEs were recorded at every study visit. AEs were reported as the worst CTCAE grade for the subject for each specific event, and are presented irrespective of relationship to treatment unless specified. The TEAE categories presented are:

- Fatal TEAEs
- Serious nonfatal TEAEs
- TEAEs leading to treatment discontinuation or dose modification
- TEAEs of special interest
- Common TEAEs (reported for at least 20% of subjects)
- Grade 3 or higher TEAEs

The Applicant's Position:

AE categorization is consistent with that used commonly in Oncology clinical studies.

The FDA's Assessment:

For increased sensitivity of AE reporting, the FDA used a combination of individual MedDRA PTs and custom groupings of PTs, as defined in Appendix 19.5, which was adopted by the Applicant for reporting of safety results in labeling. Of note, the FDA analysis of safety does not distinguish between AEs that were determined to be "related" or "unrelated" to study treatment by Investigator, and all treatment-emergent AEs, regardless of causality, are reported.

Routine Clinical Tests

Data:

Hematology and clinical chemistry tests, urinalysis, vital sign measurements, ECGs, and physical examinations were performed in E7777 clinical studies. There were minor differences in per-protocol time points for clinical tests across the studies. Test results were reviewed before administration of E7777 at the beginning of each treatment cycle.

The Applicant's Position:

Routine clinical tests used in E7777 studies were consistent with those used commonly in Oncology clinical trials.

The FDA's Assessment:

The FDA agrees with the Applicant's statement regarding hematology and clinical chemistry tests, urinalysis, vital sign measurements, ECGs, and physical examinations. However, routine baseline ophthalmic examinations, which were originally outlined in the protocol for Study 302, were removed during a protocol amendment and were not conducted in patients enrolled in

the trial.

8.2.4. Safety Results

Deaths

Data:

There were no fatal TEAEs within 30 days of the last dose of E7777, except for disease progression, in the Study 302 Stage I-III Safety Set. There was 1 fatal TEAE not related to disease progression in the Study 302 Stage I-IV Safety Set and an additional 1 fatal TEAE not related to disease progression in Study 205.

In Study 302, a 76-year old white woman with Stage IV CTCL had a fatal TEAE of acute kidney injury on Study Day 54, which the investigator considered possibly related to study treatment. This subject had experienced nonfatal SAEs, which the investigator considered possibly or probably related to study drug: hypotension (Grade 3, recovered), tachycardia (Grade 2, recovered), muscular weakness (Grade 2, recovered), hypoalbuminemia (Grade 2, did not recover), CLS (Grade 4, did not recover), pneumonia (Grade 4, did not recover), acute kidney injury (Grade 2, recovered), cytomegalovirus viremia (Grade 3, did not recover) and acute kidney injury (Grade 4, did not recover).

In Study 205, a 39-year old Japanese woman with Stage IV CTCL had a fatal TEAE of rhabdomyolysis on Study Day 11, which the investigator considered related to study treatment.

In ONTAK Study 11, one subject, a 72-year old male randomized to ONTAK 18 µg/kg, died on Day 31 of bibasilar pneumonia, unrelated to study drug per investigator.

The Applicant's Position:

None of the deaths reported in the E7777 clinical studies indicate potential new safety concerns.

The FDA's Assessment:

The FDA disagrees with the Applicant's assessment of attribution of the fatal AE in Study 302 described above for the 76-year old female with Stage IV CTCL. Based on the information available, there is a temporal relationship with the event of Grade 4 capillary leak syndrome and the fatal outcome reported as acute kidney injury. Therefore, based on FDA adjudication and known risk of capillary leak syndrome with E7777, this fatal event is considered a fatal adverse reaction and will be included in the USPI.

Serious Adverse Events

Data:

In the Study 302 Stage I-III Safety Set, nonfatal SAEs were reported for 37.7% of subjects. In the Study 302 Stage I-III Safety Set, the most frequently reported nonfatal SAEs ($\geq 4\%$ of subjects) were CLS, infusion-related reaction, and staphylococcal bacteremia. The overall incidence and type of nonfatal SAEs occurring in 2% or more of subjects in the Study 302 Stage I-III Safety Set were similar among the safety sets (Table 17). The incidences of nonfatal SAEs of increased alanine transaminase (ALT) and increased aspartate transaminase (AST) were higher in the All CTCL/PTCL Safety Set than in the Study 302 Stage I-III, Study 302 Stage I-IV, and All Study/All Stage CTCL Safety Sets (4.2% vs 0%, 0%, and 0.8% for both events).

Table 17: E7777: Summary of Serious Adverse Events Occurring in 2% or More of Subjects in Any Safety Analysis Set

MedDRA Preferred Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
<i>Subjects With Any Nonfatal SAE</i>	26 (37.7)	36 (36.7)	45 (37.8)	56 (39.4)
Capillary leak syndrome	7 (10.1)	11 (11.2)	15 (12.6)	15 (10.6)
Infusion related reaction	6 (8.7)	8 (8.2)	8 (6.7)	8 (5.6)
Staphylococcal bacteraemia	3 (4.3)	3 (3.1)	3 (2.5)	3 (2.1)
Pyrexia	2 (2.9)	2 (2.0)	2 (1.7)	5 (3.5)
Sepsis	2 (2.9)	3 (3.1)	3 (2.5)	3 (2.1)

Percentages are based on the total number of subjects in the relevant safety set.

Adverse event terms were coded using MedDRA version 24.1. MedDRA preferred terms “Neoplasm Progression,” “Malignant Neoplasm Progression,” and “Disease Progression,” which are unrelated to the study drug, are excluded.

Display is in decreasing order of preferred terms for nonfatal SAEs within the Stage I-III Safety Set. Preferred terms are only included in this table if they occurred within the percentage cutoff for the Stage I-III Safety Set.

CTCL= cutaneous T-cell lymphoma, MedDRA = Medical Dictionary for Regulatory Activities, PTCL = peripheral T-cell lymphoma, SAE = serious adverse event.

In pooled data from the 9 $\mu\text{g}/\text{kg}$ and 18 $\mu\text{g}/\text{kg}$ dose groups in ONTAK Study 11, SAEs were reported in 32.0% of subjects. As with E7777, the most common SAEs were CLS and symptoms consistent with infusion reaction (e.g., pyrexia, fatigue, and myalgia).

The Applicant’s Position:

The most commonly reported SAEs were CLS and infusion related reaction. Overall, SAEs were consistent across the E7777 safety datasets and with the ONTAK Study 11 safety profile.

The FDA’s Assessment:

The most common SAEs in the All Stage CTCL population were capillary leak syndrome, infusion related reactions, and sepsis. The rates and types of SAEs seen across the 3 safety populations were similar. Additional SAEs included skin infection, fever, rash, pneumonia, renal insufficiency, and mental status changes.

Table 18: FDA Summary of Serious Adverse Events

FDA Group Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)
<i>Subjects with any nonfatal SAE</i>	26 (37.7)	36 (36.7)	45 (37.8)
Capillary leak syndrome	7 (10.1)	11 (11.2)	15 (12.6)
Infusion related reaction	6 (8.7)	8 (8.2)	8 (6.7)
Sepsis	5 (7.2)	6 (6.1)	6 (5)
Skin Infection	2 (2.9)	3 (3.1)	3 (2.5)
Fever	2 (2.9)	2 (2)	2 (1.7)
Rash	2 (2.9)	2 (2.0)	2 (1.7)
Pneumonia	1 (1.4)	2 (2)	3 (2.5)
Renal Insufficiency	1 (1.4)	3 (3.1)	3 (2.5)
Mental status changes	0 (0)	2 (2)	3 (2.5)

Source: FDA analysis based on ADAE.xpt

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

In the Study 302 Stage I-III Safety Set, the overall incidence of TEAEs leading to discontinuation of E7777 was 11.6%. The TEAE of CLS led to discontinuation of E7777 in 3 (4.3%) subjects. All other TEAEs leading to E7777 discontinuation were each reported in 1 subject. There were no notable differences among the safety sets with respect to TEAEs leading to discontinuation (Table 19).

Table 19: E7777: Summary of Adverse Events Leading to Treatment Discontinuation

MedDRA Preferred Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
<i>Subjects With Any TEAEs Leading to Treatment Discontinuation of E7777</i>	8 (11.6)	13 (13.3)	18 (15.1)	23 (16.2)
Capillary leak syndrome	3 (4.3)	3 (3.1)	3 (2.5)	3 (2.1)
Acute kidney injury	1 (1.4)	2 (2.0)	2 (1.7)	2 (1.4)
Infusion related reaction	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)
Periorbital oedema	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)
Respiratory failure	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)
Staphylococcal bacteraemia	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)
Supraventricular tachycardia	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)
Tumour flare	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)
Vision blurred	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)

Table 19: E7777: Summary of Adverse Events Leading to Treatment Discontinuation

MedDRA Preferred Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)

Percentages are based on the total number of subjects in the relevant safety set.
Adverse event terms were coded using MedDRA version 24.1. MedDRA preferred terms “Neoplasm Progression,” “Malignant Neoplasm Progression,” and “Disease Progression,” which are unrelated to the study drug, are excluded. Display is in decreasing order of preferred terms within the Study 302 Stage I-III Safety Set.
CTCL= cutaneous T-cell lymphoma, MedDRA = Medical Dictionary for Regulatory Activities, PTCL = peripheral T-cell lymphoma, TEAE = treatment-emergent adverse event.

The incidence of TEAEs leading to discontinuation in ONTAK Study 11 was 20.0%. The most common TEAEs leading to discontinuation were fatigue and asthenia; CLS was also reported.

The Applicant’s Position:

The only TEAE leading to discontinuation of E7777 in more than 1 subject was CLS. Overall, TEAEs leading to discontinuation of E7777 were consistent across the E7777 safety datasets and with the ONTAK Study 11 safety profile.

The FDA’s Assessment:

In the All Stage CTCL safety population, 15.1% of patients permanently discontinued study treatment due to an AE. The most common AE leading to treatment discontinuation was capillary leak syndrome in 3 patients (2.5%). Additional AEs leading to treatment discontinuation across all 3 safety populations included infusion-related reaction, renal insufficiency, respiratory failure, sepsis, pneumonia, and mental status changes.

Table 20: FDA Summary of Adverse Events Leading to Treatment Discontinuation

FDA Group Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)
<i>Subjects with any TEAEs leading to treatment discontinuation</i>	8 (11.6)	13 (13.3)	18 (15.1)
Capillary leak syndrome	3 (4.3)	3 (3.1)	3 (2.5)
Infusion related reaction	1 (1.4)	1 (1.0)	1 (0.8)
Renal Insufficiency	1 (1.4)	2 (2.0)	2 (1.7)
Respiratory failure	1 (1.4)	1 (1.0)	1 (0.8)
Sepsis	1 (1.4)	1 (1.0)	1 (0.8)
Pneumonia	0 (0)	N/A	1 (0.8) 3 (2.5)
Mental Status Changes	0 (0)	2 (2.0)	

Source: FDA analysis based on ADAE.xpt

Dose Interruption/Reduction Due to Adverse Effects

Data:

In each E7777 study protocol, drug interruption and dose reduction guidelines for E7777 for the management of treatment-related toxicity were specified.

In the Study 302 Stage I-III Safety Set, 37.7% of subjects had a TEAE leading to an E7777 drug interruption, and 4.3% had a TEAE leading to an E7777 dose reduction. The TEAEs that most frequently led to an E7777 drug interruption were CLS and infusion-related reaction. Other common ($\geq 5\%$) TEAEs that led to drug interruption were increased weight, nausea, and tachycardia. There were no notable differences among the safety sets with respect to TEAEs leading to drug interruption (Table 21).

The TEAE of CLS led to dose reduction of E7777 in 2 (2.9%) subjects. The other 2 TEAEs leading to E7777 dose reduction (increased transaminases and myalgia) were each reported in 1 subject. There were no notable differences among the safety sets with respect to TEAEs leading to dose reduction.

MedDRA Preferred Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
<i>Subjects With Any TEAE Leading to Drug Interruption</i>	26 (37.7)	36 (36.7)	39 (32.8)	42 (29.6)
Capillary leak syndrome	6 (8.7)	9 (9.2)	10 (8.4)	10 (7.0)
Infusion related reaction	6 (8.7)	7 (7.1)	7 (5.9)	7 (4.9)
Weight increased	5 (7.2)	6 (6.1)	6 (5.0)	6 (4.2)
Nausea	4 (5.8)	5 (5.1)	5 (4.2)	5 (3.5)
Tachycardia	4 (5.8)	4 (4.1)	4 (3.4)	4 (2.8)
Diarrhoea	3 (4.3)	3 (3.1)	3 (2.5)	3 (2.1)
Pyrexia	3 (4.3)	3 (3.1)	3 (2.5)	3 (2.1)
Chills	2 (2.9)	2 (2.0)	2 (1.7)	2 (1.4)
Hypoalbuminaemia	2 (2.9)	3 (3.1)	4 (3.4)	4 (2.8)
<i>Subjects With Any TEAE Leading to Dose Reduction</i>	3 (4.3)	3 (3.1)	5 (4.2)	7 (4.9)
Capillary leak syndrome	2 (2.9)	2 (2.0)	2 (1.7)	2 (1.4)
Myalgia	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)
Increased transaminases	1 (1.4)	1 (1.0)	1 (0.8)	1 (0.7)

Percentages are based on the total number of subjects in the relevant safety sets.

Adverse event terms were coded using MedDRA version 24.1. MedDRA preferred terms "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression," which are unrelated to the study drug, are excluded. Display is in decreasing order of preferred terms for TEAEs leading to drug interruption within the Stage I-III Safety Set. Preferred terms are only included in this table if they occurred within the percentage cutoff for the Stage I-III Safety Set.

CTCL= cutaneous T-cell lymphoma, MedDRA = Medical Dictionary for Regulatory Activities, PTCL = peripheral T-cell lymphoma, TEAE = treatment-emergent adverse event.

Drug interruptions and dose reductions were not reported in ONTAK Study 11.

The Applicant’s Position:

The TEAEs most frequently leading to E7777 drug interruption were CLS and infusion-related reaction, and the TEAE most frequently leading to dose reduction was CLS. These findings were consistent across the E7777 safety datasets.

The FDA’s Assessment:

In the All Stage CTCL safety population, 5 (4.2%) patients had dose reductions of study treatment due to AEs. AEs leading to dose reduction that occurred in one or more patients were capillary leak syndrome, transaminase elevation, musculoskeletal pain and rash. The table below shows the AEs leading to dose reduction in each safety population.

In the All Stage CTCL safety population, 39 (32.8%) patients interrupted study treatment due to an AE. The most common AEs leading to treatment interruption were capillary leak syndrome, infusion related reaction, increased weight, nausea, tachycardia, diarrhea, fever, hypoalbuminemia, and edema.

Table 22: FDA Summary of Adverse Events Leading to Dose Reduction or Interruption

FDA Group Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)
<i>Subjects with any TEAE Leading to Dose Reduction</i>	3 (4.3)	3 (3.1)	5 (4.2)
Capillary leak syndrome	2 (2.9)	2 (2.0)	2 (1.7)
Transaminase elevation	1 (1.4)	1 (1.0)	2 (1.7)
Musculoskeletal pain	1 (1.4)	1 (1.0)	1 (0.8)
Rash	N/A	N/A	1 (0.8)
<i>Subjects with any TEAE Leading to Drug Interruption</i>	26 (37.7)	36 (36.7)	39 (32.8)
Capillary leak syndrome	6 (8.7)	9 (9.2)	10 (8.4)
Infusion related reaction	6 (8.7)	7 (7.1)	7 (5.9)
Weight increased	5 (7.2)	6 (6.1)	6 (5.0)
Nausea	4 (5.8)	5 (5.1)	5 (4.2)
Tachycardia	4 (5.8)	4 (4.1)	4 (3.4)
Diarrhea	3 (4.3)	3 (3.1)	3 (2.5)

Fever	3 (4.3)	3 (3.1)	3 (2.5)
Hypoalbuminemia	2 (2.9)	3 (3.1)	4 (3.4)
Edema	1 (1.4)	3 (3.1)	3 (2.5)

Source: FDA analysis based on ADAE.xpt

Significant Adverse Events

Data:

Adverse Events of Special Interest

AEs of special interest (AESI) for E7777 were predefined based on the ONTAK Study 11 safety profile. Clinically, the most important AESIs are CLS, infusion reactions, visual impairment, and hepatotoxicity, which are reviewed here. Other AESIs are hypersensitivity, rash, infection, and thrombotic events. The worst CTCAE grade was reported for each event for any subject. In the Study 302 Stage I-III Safety Set, the occurrence of AESIs was highest in the first cycle, declined in Cycles 2 and 3, and thereafter occurred in very few subjects.

Capillary Leak Syndrome

In the Study 302 Stage I-III Safety Set, 20.3% of subjects met the criteria for the AESI of CLS (defined as preferred term [PT] of CLS and/or TEAEs in at least 2 of 3 categories assessing hypotension, edema, and hypoalbuminemia, similar to that defined in the ONTAK US prescribing information [USPI]), all of which were considered treatment related. The most common PTs that contributed to the AESI category of CLS were CLS (17.4%), peripheral edema (5.8%), and hypoalbuminemia (4.3%). There was 1 Grade 4 CLS event, considered related to study drug, and no Grade 5 events. CLS SAEs and TEAEs leading to study drug discontinuation were reported for 10.1% and 4.3% of subjects, respectively. TEAEs leading to study drug interruption or dose reduction were reported for 6 (8.7%) and 2 (2.9%) subjects, respectively. Similar results were observed for the other 3 safety sets, with a slightly higher incidence of the AESI of CLS reported in the All CTCL/PTCL Safety Set (28.9%).

The ONTAK USPI defines CLS as the occurrence of at least 2 of the following 3 symptoms: hypotension, edema, and serum albumin < 3.0 g/dL). CLS was reported in 32.5% of ONTAK treated subjects in 3 studies; one-third required hospitalization or medical intervention to prevent hospitalization.

Hepatotoxicity

The criteria for the AESI of hepatotoxicity included PTs in the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) of Drug related hepatic disorders, comprehensive search (narrow scope), and the additional PTs of encephalopathy and metabolic encephalopathy. In the Study 302 Stage I-III Safety Set, 36.2% of subjects had a TEAE that met the criteria for the AESI category of hepatotoxicity, all of which were considered treatment-related. Most of these events were Grade 1 or 2, with the remainder Grade 3 (11.6%). The most common TEAEs in the hepatotoxicity category were increased ALT (27.5%, 19 subjects);

increased AST (26.1%, 18 subjects); increased blood bilirubin and increased transaminases (4.3%, 3 subjects each). There were no SAEs of hepatotoxicity. None of the hepatotoxicity TEAEs led to study drug discontinuation and only 2.9% subjects had hepatotoxicity TEAEs leading to study drug interruption or reduction.

The incidence of the AESI of hepatotoxicity was generally similar for the other 3 safety sets, although higher in the All CTCL/PTCL Safety Set (51.4%, and 28.9% Grade 3 or higher).

In ONTAK Study 11, the incidence of increased ALT and increased AST lab values that shifted from Grade 0-2 at baseline to Grade $\geq$ 3 on treatment were 28.0% and 7.0% respectively.

Visual Impairment

In the Study 302 Stage I-III Safety Set, 9 (13.0%) subjects had a TEAE that met the criteria for the AESI category of visual impairment, all coded to the PT of "vision blurred;" 8 were Grade 1, and 1 was Grade 2. The TEAEs in 5 (7.2%) subjects were considered treatment related. SAEs and TEAEs of visual impairment leading to study drug discontinuation were reported each for 1 (1.4%) subject. TEAEs leading to drug interruption were reported for 1 (1.4%) subject. Similar results were observed for the other 3 safety sets, with additional TEAEs of photopsia and visual impairment reported in 1 subject in the All CTCL/PTCL Safety Set.

Visual acuity and color vision assessments were performed in the Lead-In part of Study 302. An independent ophthalmologist's evaluation of these data indicated that there was no apparent correlation between loss of vision or color vision and the incidence of the reported vision related TEAEs during exposure to E7777.

In conclusion, the TEAEs of visual impairment did not indicate a dose-dependent or cumulative toxicity after administration of E7777 in subjects with CTCL or PTCL. No severe or serious TEAEs of visual impairment were reported.

The ONTAK USPI has a safety warning for loss of visual acuity, usually with loss of color vision, with or without pigment mottling following administration of ONTAK. There were 2 SAEs and 2 non-serious AEs of visual loss in ONTAK clinical trials; in addition, 3 case reports of visual loss were published in the postmarketing period. The warning was added to the USPI in 2006.

Infusion Reactions

In the Study 302 Stage I-III Safety Set, 73.9% of subjects had a TEAE that met the criteria for the AESI category of infusion reactions, of which TEAEs in 68.1% of subjects were considered treatment related. The majority of these events were Grade 1 or 2, and the rest were Grade 3 (4.3%). SAEs and TEAEs leading to study drug discontinuation that met the criteria for the AESI category of infusion reactions were reported for 7.2% and 1.4% of subjects, respectively. TEAEs leading to study drug interruption or dose reduction were reported for 10.1% and 1.4% of subjects, respectively. Similar results were observed for the other 3 safety sets.

The most common TEAEs that contributed to the AESI of infusion reactions included nausea, fatigue, chills, and infusion related reaction, all reported in >20% of subjects. In ONTAK Study 11, infusion-related TEAEs of “flu-like syndrome” were reported in 80.0% of ONTAK-treated subjects.

The frequency, severity and type of AESIs for E7777 were consistent across the E7777 safety datasets and with the ONTAK Study 11 safety profile, except for visual loss, for which there have been no reports of severe or serious TEAEs in E7777 clinical studies or postmarketing data.

The FDA’s Assessment:

The AESIs were evaluated and the prior clinical experience of ONTAK was considered to provide additional context. The selected list of AESIs is comprised of capillary leak syndrome, hepatotoxicity, hypersensitivity, infection, infusion-related reaction, and visual impairment. Detailed analyses of the AESIs warranting a more thorough evaluation are provided below for two safety populations (Study 302 Stage I-IV and All Stage CTCL).

Capillary Leak Syndrome

Capillary leak syndrome (CLS) was defined in the clinical trials as the occurrence of at least 2 of the following symptoms at any time during E7777 therapy: hypotension, edema, and serum albumin < 3 g/dL. In the All Stage CTCL population, there was a 26.9% incidence of any-grade CLS, with a 9.2% incidence of Grade ≥ 3 CLS. A summary of the symptoms of CLS that occurred in ≥ 1% of the All Stage CTCL population are shown in Table 23 below. The most common CLS manifestations included edema, hypoalbuminemia, and hypotension. Pleural effusion, pericardial effusion and dehydration also occurred. There was one (0.8%) fatal occurrence of CLS, as described earlier.

Table 23: FDA Summary of Capillary Leak Syndrome

FDA Group Term	Study 302 Stage I-IV (N=98) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)	All Study/All Stage CTCL (N=119) n (%)
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Subjects with any capillary leak syndrome	23 (23.5)	7 (7.1)	32 (26.9)	11 (9.2)
CLS	19 (19.4)	6 (6.1)	24 (20.2)	10 (8.4)
Dehydration	1 (1.0)	0 (0.0)	1 (0.8)	0 (0.0)
Hypernatremia	1 (1.0)	0 (0.0)	1 (0.8)	0 (0.0)

<i>Hypoalbuminemia</i>	6 (6.1)	0 (0.0)	12 (10.1)	1 (0.8)
<i>Hypotension</i>	4 (4.1)	3 (3.1)	5 (4.2)	3 (2.5)
<i>Edema</i>	8 (8.2)	0 (0.0)	13 (10.9)	1 (0.8)
<i>Pericardial effusion</i>	1 (1.0)	0 (0.0)	1 (0.8)	0 (0.0)
<i>Pleural effusion</i>	2 (2.0)	0 (0.0)	2 (1.7)	0 (0.0)

Source: FDA analysis based on ADAE.xpt

Because of the risk of CLS and the severity, including a fatal case, CLS will be included in a boxed warning in the USPI.

Hepatotoxicity

In the All Stage CTCL population, hepatotoxicity adverse events were reported in 43.7% of patients, with 20.2% incidence of Grade ≥ 3 hepatotoxicity. Transaminase elevation was the most common TEAE in the hepatotoxicity category, and occurred in 42% of patients with 19.3% having Grade ≥ 3 toxicity. Notably, the AE data underrepresents the incidence of transaminase elevation as show in the table below. Importantly, there were no cases of Hy’s law in the safety population following FDA review of the available data.

Table 24: FDA Summary of Hepatotoxicity

FDA Group Term	Study 302 Stage I-IV (N=98) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)	All Study/All Stage CTCL (N=119) n (%)
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Subjects with any hepatotoxicity	34 (34.7)	10 (10.2)	52 (43.7)	24 (20.2)
<i>Transaminase elevation</i>	32 (32.7)	10 (10.2)	50 (42.0)	23 (19.3)
<i>Hyperbilirubinemia</i>	3 (3.1)	1 (1.0)	3 (2.5)	1 (0.8)
<i>Hepatitis</i>	1 (1.0)	0 (0.0)	1 (0.8)	0 (0.0)
<i>ALT Elevation*</i>	62 (64.6)	13 (13.5)	81 (69.8)	26 (22.4)
<i>AST Elevation*</i>	55 (57.3)	3 (3.1)	74 (63.8)	10 (8.6)
<i>Bilirubin Increased*</i>	4 (4.2)	1 (1.1)	6 (5.2)	1 (0.9)

*Based on laboratory data

Source: FDA analysis based on ADAE.xpt

Based on the incidence of hepatotoxicity and the need for appropriate monitoring, hepatotoxicity was included as a Warning & Precaution in the USPI.

Hypersensitivity

In the All Stage CTCL population, there was a 63% incidence of hypersensitivity in patients, with 11.8% of patients having Grade ≥ 3 toxicity. The most common TEAEs constituting hypersensitivity were rash, infusion-related reaction, and fever.

Table 25: FDA Summary of Hypersensitivity

FDA Group Term	Study 302 Stage I-IV (N=98) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)	All Study/All Stage CTCL (N=119) n (%)
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Subjects with any hypersensitivity	62 (63.3)	13 (13.3)	75 (63)	14 (11.8)
<i>Arthralgia</i>	5 (5.1)	0 (0.0)	6 (5.0)	0 (0.0)
<i>Chest pain</i>	2 (2.0)	0 (0.0)	2 (1.7)	0 (0.0)
<i>Chills</i>	22 (22.4)	1 (1.0)	22 (18.5)	1 (0.8)
<i>Dermatitis contact</i>	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
<i>Rash</i>	18 (18.4)	2 (2.0)	19 (16.0)	2 (1.7)
<i>Dry skin</i>	2 (2.0)	0 (0.0)	2 (1.7)	0 (0.0)
<i>Dyspnea</i>	7 (7.1)	0 (0.0)	7 (5.9)	0 (0.0)
<i>Edema</i>	3 (3.1)	0 (0.0)	3 (2.5)	0 (0.0)
<i>Hypotension</i>	6 (6.1)	3 (3.1)	7 (5.9)	3 (2.5)
<i>Infusion related reaction</i>	21 (21.4)	6 (6.1)	21 (17.6)	6 (5.0)
<i>Musculoskeletal pain</i>	6 (6.1)	1 (1.0)	10 (8.4)	1 (0.8)
<i>Pain</i>	2 (2.0)	0 (0.0)	3 (2.5)	1 (0.8)

<i>Palpitations</i>	1 (1.0)	0 (0.0)	1 (0.8)	0 (0.0)
<i>Periorbital edema</i>	2 (2.0)	0 (0.0)	2 (1.7)	0 (0.0)
<i>Fever</i>	10 (10.2)	0 (0.0)	17 (14.3)	0 (0.0)
<i>Tachycardia</i>	5 (5.1)	1 (0.0)	5 (4.2)	1 (0.8)

Source: FDA analysis based on ADAE.xpt

Infections

In the All Stage CTCL population, there was a 12.6% incidence of any-grade and Grade ≥ 3 infection. A summary of the types of infections that occurred in $\geq 1\%$ of the All Stage CTCL population are shown in the table below. Sepsis occurred in 4.2% of patients in the All Stage CTCL safety group.

Table 26: FDA Summary of Infections

FDA Group Term	Study 302 Stage I-IV (N=98) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)	All Study/All Stage CTCL (N=119) n (%)
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Subjects with any infections	13 (13.3)	13 (13.3)	15 (12.6)	15 (12.6)
<i>Cytomegalovirus infection</i>	1 (1.0)	1 (1.0)	1 (0.8)	1 (0.8)
<i>Herpes virus infection</i>	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
<i>Herpes zoster meningoencephalitis</i>	1 (1.0)	1 (1.0)	1 (0.8)	1 (0.8)
<i>Herpes zoster oticus</i>	1 (1.0)	1 (1.0)	1 (0.8)	1 (0.8)
<i>Otitis externa</i>	1 (1.0)	1 (1.0)	1 (0.8)	1 (0.8)
<i>Pneumonia</i>	1 (1.0)	1 (1.0)	2 (1.7)	2 (1.7)
<i>Post herpetic neuralgia</i>	1 (1.0)	1 (1.0)	1 (0.8)	1 (0.8)
<i>Sepsis</i>	5 (5.1)	5 (5.1)	5 (4.2)	5 (4.2)
<i>Skin infection</i>	2 (2.0)	2 (2.0)	2 (1.7)	2 (1.7)

<i>Tooth infection</i>	1 (1.0)	1 (1.0)	1 (0.8)	1 (0.8)
<i>Upper respiratory tract infection</i>	2 (2.0)	2 (2.0)	2 (1.7)	2 (1.7)
<i>Urinary tract infection</i>	2 (2.0)	2 (2.0)	2 (1.7)	2 (1.7)

Source: FDA analysis based on ADAE.xpt

Infusion-Related Reaction

In the All Stage CTCL population, there was a 69% incidence of any-grade infusion-related reaction (IRR), with a 3.4% incidence of Grade $\geq$ 3 IRR. The predominant manifestations of IRR included nausea, fatigue, chills, musculoskeletal pain, vomiting, fever and arthralgia.

Table 27: FDA Summary of Infusion-related Reaction

FDA Group Term	Study 302 Stage I-IV (N=98) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)	All Study/All Stage CTCL (N=119) n (%)
	Any Grade	Grade $\geq$ 3	Any Grade	Grade $\geq$ 3
Subjects with any infusion-related reactions	69 (70.4)	4 (4.1)	82 (69.0)	4 (3.4)
<i>Arthralgia</i>	5 (5.1)	0 (0.0)	6 (5.0)	0 (0.0)
<i>Fatigue</i>	22 (22.4)	0 (0.0)	24 (20.2)	0 (0.0)
<i>Chills</i>	21 (21.4)	1 (1.0)	21 (17.6)	1 (0.8)
<i>Respiratory tract infection</i>	2 (2.0)	0 (0.0)	2 (1.7)	0 (0.0)
<i>Infusion related reaction</i>	19 (19.4)	3 (3.1)	19 (16.0)	3 (2.5)
<i>Musculoskeletal pain</i>	5 (5.1)	0 (0.0)	7 (5.9)	0 (0.0)
<i>Nausea</i>	33 (33.7)	0 (0.0)	39 (32.8)	0 (0.0)
<i>Fever</i>	7 (7.1)	0 (0.0)	12 (10.1)	0 (0.0)
<i>Vomiting</i>	8 (8.2)	0 (0.0)	10 (8.4)	0 (0.0)
<i>Malaise</i>	0 (0.0)	0 (0.0)	8 (6.7)	0 (0.0)

Source: FDA analysis based on ADAE.xpt

Based on the severity and risk of infusion-related reactions and the need to for appropriate management, infusion-related reactions were included as a Warning and Precaution in the USPI.

Visual Impairment

In the All Stage CTCL population, there was a 9.2% incidence of visual impairment, with Grade 1 in 8% and Grade 2 in 1%. The most commonly reported symptom was blurred vision. One patient reported photopsia.

Table 28: FDA Summary of Visual Impairment

FDA Group Term	Study 302 Stage I-IV (N=98) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)	All Study/All Stage CTCL (N=119) n (%)
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Subjects with any visual impairment	9 (9.2)	0 (0.0)	11 (9.2)	0 (0.0)
<i>Vision blurred</i>	9 (9.2)	0 (0.0)	11 (9.2)	0 (0.0)
<i>Photopsia</i>	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

Source: FDA analysis based on ADAE.xpt

Treatment-emergent Adverse Events and Adverse Reactions

Data:

Nearly all subjects in the Study 302 Stage I-III Safety Set had at least 1 TEAE and at least 1 treatment related TEAE. Treatment-emergent “adverse reactions” are synonymous with “treatment-related” TEAEs, and are defined as TEAEs that were considered by the Investigator to be related, possibly related, or probably related to study drug or TEAEs with a missing causality assessment. Most subjects with TEAEs had events that were Grade 1 or 2, and those Grade ≥3 were almost all Grade 3, with a few Grade 4 events and no Grade 5 events. The incidences of treatment-related TEAEs, SAEs, and TEAEs leading to study drug interruption, reduction, or discontinuation in the Study 302 Stage I-III Safety Set were generally similar to the incidences seen in the other 3 safety sets (Table 29).

In the Study 302 Stage I-III Safety Set, there was a higher incidence of TEAEs leading to drug interruption of E7777 (37.7%) than of TEAEs leading to discontinuation of E7777 (11.6%); there were few subjects with dose reduction (4.3%). Similar results were observed in the other 3

safety sets. These findings suggest that most TEAEs can be managed through dose modification, especially drug interruption, rather than discontinuation.

Table 29: Summary of Treatment-Emergent Adverse Events

Subjects with at Least 1 of the Following:	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
Subjects with Any TEAEs	68 (98.6)	97 (99.0)	118 (99.2)	141 (99.3)
Subjects with Any TEAEs with Worst CTCAE Grade ^a of				
≥3	30 (43.5)	43 (43.9)	62 (52.1)	84 (59.2)
3	27 (39.1)	37 (37.8)	49 (41.2)	59 (41.5)
4	3 (4.3)	5 (5.1)	11 (9.2)	23 (16.2)
5	0	1 (1.0)	2 (1.7)	2 (1.4)
Subjects with Any Treatment-Related TEAEs ^{a,b}	65 (94.2)	92 (93.9)	113 (95.0)	136 (95.8)
Subjects with Any Treatment-Related TEAEs with Worst CTCAE Grade of ^{a,b}				
≥3	21 (30.4)	34 (34.7)	53 (44.5)	75 (52.8)
3	20 (29.0)	30 (30.6)	42 (35.3)	53 (37.3)
4	1 (1.4)	3 (3.1)	9 (7.6)	20 (14.1)
5	0	1 (1.0)	2 (1.7)	2 (1.4)
Subjects with Any SAEs	26 (37.7)	36 (36.7)	45 (37.8)	56 (39.4)
Subjects with Any Nonfatal SAEs	26 (37.7)	36 (36.7)	45 (37.8)	56 (39.4)
Subjects with Any TEAEs Leading to Study Drug Adjustment ^c				
Study Drug Discontinuation	8 (11.6)	13 (13.3)	18 (15.1)	23 (16.2)
Study Drug Dose Interruption or Reduction	26 (37.7)	36 (36.7)	40 (33.6)	44 (31.0)
Study Drug Interruption	26 (37.7)	36 (36.7)	39 (32.8)	42 (29.6)
Study Drug Dose Reduction	3 (4.3)	3 (3.1)	5 (4.2)	7 (4.9)

Percentages are based on the total number of subjects in the relevant safety set.

MedDRA preferred terms “Neoplasm Progression,” “Malignant Neoplasm Progression,” and “Disease Progression,” which are unrelated to the study drug, are excluded.

For each row/category, subjects with 2 or more adverse events in that category are counted only once.

The TEAEs, including SAEs, used the window of 30 days for Studies 302 and 101, and 37 days for Study 205 after the last dose of study drug per protocol.

CTCAE = Common Terminology Criteria for Adverse Events, CTCL= cutaneous T-cell lymphoma, MedDRA = Medical Dictionary for Regulatory Activities, PTCL = peripheral T-cell lymphoma, SAE = serious adverse event, TEAE = treatment-emergent adverse event.

a: Adverse events were graded using the CTCAE version in effect at the time the event occurred: version 4.0 for Study 101, version 4.03 for Study 205, and version 4.03 or version 5 for Study 302 (version changed from 4.03 to 5 with Protocol Amendment 5 [03 May 2018]). If a subject had more than 1 TEAE, the subject was only counted once at the worst grade.

b: Treatment-related TEAEs include TEAEs that were considered by the Investigator to be related, possibly related, or probably related to study drug or TEAEs with a missing causality.

c: Subjects may be counted in multiple categories.

The most commonly reported TEAEs were nausea, fatigue, increased ALT, chills, peripheral edema, increased AST, infusion-related reaction, and headache. The incidence and type of TEAEs observed were generally consistent across the safety sets (Table 30).

Table 30: Treatment-Emergent Adverse Events Occurring in at Least 10% of Subjects by Preferred Term and in Decreasing frequency in Any Safety Set

MedDRA Preferred Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
<i>Subjects With at Least 1 TEAE</i>	68 (98.6)	97 (99.0)	118 (99.2)	141 (99.3)
Nausea	30 (43.5)	39 (39.8)	47 (39.5)	54 (38.0)
Fatigue	22 (31.9)	29 (29.6)	32 (26.9)	38 (26.8)
Alanine aminotransferase increased	19 (27.5)	27 (27.6)	45 (37.8)	65 (45.8)
Chills	19 (27.5)	26 (26.5)	26 (21.8)	26 (18.3)
Oedema peripheral	19 (27.5)	28 (28.6)	32 (26.9)	38 (26.8)
Aspartate aminotransferase increased	18 (26.1)	26 (26.5)	44 (37.0)	65 (45.8)
Infusion related reaction	17 (24.6)	22 (22.4)	22 (18.5)	22 (15.5)
Headache	16 (23.2)	18 (18.4)	20 (16.8)	21 (14.8)
Diarrhoea	13 (18.8)	19 (19.4)	19 (16.0)	22 (15.5)
Pruritus	13 (18.8)	16 (16.3)	18 (15.1)	18 (12.7)
Capillary leak syndrome	12 (17.4)	19 (19.4)	24 (20.2)	25 (17.6)
Pyrexia	11 (15.9)	17 (17.3)	25 (21.0)	40 (28.2)
Hypoalbuminaemia	10 (14.5)	17 (17.3)	33 (27.7)	48 (33.8)
Decreased appetite	9 (13.0)	16 (16.3)	23 (19.3)	32 (22.5)
Dizziness	9 (13.0)	9 (9.2)	11 (9.2)	11 (7.7)
Vision blurred	9 (13.0)	9 (9.2)	11 (9.2)	11 (7.7)
Vomiting	9 (13.0)	13 (13.3)	17 (14.3)	22 (15.5)
Weight increased	9 (13.0)	14 (14.3)	18 (15.1)	22 (15.5)
Arthralgia	8 (11.6)	8 (8.2)	9 (7.6)	10 (7.0)
Constipation	8 (11.6)	15 (15.3)	26 (21.8)	32 (22.5)
Myalgia	8 (11.6)	9 (9.2)	13 (10.9)	14 (9.9)
Back pain	7 (10.1)	8 (8.2)	10 (8.4)	12 (8.5)
Insomnia	7 (10.1)	14 (14.3)	18 (15.1)	23 (16.2)

Percentages are based on the total number of subjects in the relevant safety set.

Adverse event terms were coded using MedDRA version 24.1. MedDRA preferred terms “Neoplasm Progression,”

“Malignant Neoplasm Progression,” and “Disease Progression,” which are unrelated to the study drug, are excluded.

Display is in decreasing order of preferred terms for the Stage I-III Safety Set. Preferred terms are only included in this table if they occurred within the percentage cutoff for the Stage I-III Safety Set.

For each row/category, subjects with 2 or more adverse events in that category are counted only once.

MedDRA Preferred Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)

CTCL= cutaneous T-cell lymphoma, MedDRA = Medical Dictionary for Regulatory Activities, PTCL = peripheral T-cell lymphoma, TEAE = treatment-emergent adverse event.

The Applicant’s Position:

The frequency, severity and type of TEAEs for E7777 were consistent across the E7777 safety datasets and with the ONTAK Study 11 safety profile.

The FDA’s Assessment:

The table below summarizes all-cause treatment-emergent AEs, excluding laboratory terms, in each safety population within the primary safety window, using a threshold of ≥ 10%. Slight differences in some AE incidences by FDA and the Applicant analysis are not unexpected due to methodologic differences.

The most common non-laboratory AEs (≥ 15%) were nausea, fatigue, edema, musculoskeletal pain, chills, infusion related reaction, headache, rash, diarrhea, pruritis, capillary leak syndrome, hypoalbuminemia, and fever.

Table 31: FDA Summary of Treatment Emergent Adverse Events in ≥ 15% of Patients

FDA Group Term	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/All Stage CTCL (N=119) n (%)
Subjects with at least 1 TEAE	68 (98.6)	97 (99.0)	118 (99.2)
Nausea	30 (43.4)	39 (39.8)	47 (39.5)
Fatigue	26 (37.7)	33 (33.7)	36 (30.3)
Transaminase elevation	23 (33.3)	32 (32.7)	50 (42.0)
Edema	23 (33.3)	34 (34.7)	42 (35.5)
Musculoskeletal Pain	19 (27.5)	25 (25.5)	31 (26.1)
Chills	19 (27.5)	26 (26.5)	26 (21.8)
Infusion related reaction	17 (24.6)	22 (22.4)	22 (18.5)
Headache	17 (24.6)	19 (19.4)	21 (17.6)
Rash	16 (23.2)	25 (25.5)	27 (22.7)
Diarrhea	13 (18.8)	19 (19.4)	19 (16.0)
Pruritis	13 (18.8)	16 (16.3)	18 (15.1)
Capillary Leak Syndrome	12 (17.4)	19 (19.4)	24 (20.2)
Hypoalbuminemia	11 (15.9)	18 (18.4)	34 (28.6)

Fever	11 (15.9)	17 (17.3)	25 (21.0)
Vision changes	9 (13.0)	9 (9.2)	11 (9.2)
Decreased Appetite	9 (13.0)	16 (16.3)	23 (19.3)
Dizziness	9 (13.0)	9 (9.2)	11 (9.2)
Vomiting	9 (13.0)	13 (13.3)	17 (14.3)
Weight increased	9 (13.0)	14 (14.3)	18 (15.1)
Mental Status Changes	9 (13.0)	13 (13.3)	15 (12.6)
Skin Infection	9 (13.0)	11 (11.2)	13 (10.9)
Arthralgia	8 (11.6)	9 (9.2)	10 (8.4)
Constipation	8 (11.6)	15 (15.3)	26 (21.8)
Renal Insufficiency	8 (11.6)	12 (12.2)	14 (11.8)
Insomnia	7 (10.1)	14 (14.3)	18 (15.1)

Source: FDA analysis based on ADAE.xpt

Other clinically relevant AEs in < 10% of patients included sepsis and peripheral neuropathy.

Laboratory Findings

Data:

Hematology

In the Study 302 Stage I-III Safety Set, there was no notable trend in changes over time in the grade of hematology parameters (i.e., hemoglobin, platelets, lymphocytes, and neutrophils). Of the shifts from Baseline, most were single-grade shifts. The overall pattern of shifts was similar across the safety sets.

Of note, shifts of an increase of ≥ 1 grade to Grade ≥ 3 postbaseline value for decreased lymphocyte count were observed for 13 subjects (20.0%) in the Study 302 Stage I-III Safety Set. Similar results were observed for the other 3 safety sets, although Grade 3 or 4 decreased platelet count and Grade 4 decreased lymphocyte count and Grade 4 decreased lymphocyte count occurred at a higher incidence in the All Study/All Stage CTCL and All CTCL/PTCL Safety Sets. A summary of hematology laboratory abnormalities is presented in Table 32.

Table 32: Hematology Laboratory Abnormalities

Hematology Parameter Worst Postbaseline Grade	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
Hemoglobin decreased, m^a	65	93	113	136
Any Grade	22 (33.8)	29 (31.2)	38 (33.6)	47 (34.6)
Grade 3 or 4	1 (1.5)	1 (1.1)	3 (2.7)	4 (2.9)
Grade 3	1 (1.5)	1 (1.1)	3 (2.7)	4 (2.9)
Grade 4	0	0	0	0

Table 32: Hematology Laboratory Abnormalities

Hematology Parameter Worst Postbaseline Grade	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
Platelet count decreased, m^a	65	92	113	136
Any Grade	5 (7.7)	6 (6.5)	13 (11.5)	30 (22.1)
Grade 3 or 4	1 (1.5)	1 (1.1)	4 (3.5)	8 (5.9)
Grade 3	1 (1.5)	1 (1.1)	3 (2.7)	4 (2.9)
Grade 4	0	0	1 (0.9)	4 (2.9)
Lymphocyte count decreased m^a	65	93	113	136
Any Grade	34 (52.3)	44 (47.3)	58 (51.3)	79 (58.1)
Grade 3 or 4	13 (20.0)	17 (18.3)	26 (23.0)	43 (31.6)
Grade 3	12 (18.5)	14 (15.1)	19 (16.8)	27 (19.9)
Grade 4	1 (1.5)	3 (3.2)	7 (6.2)	16 (11.8)
Lymphocyte count increased m^a	65	93	113	136
Any Grade	5 (7.7)	10 (10.8)	11 (9.7)	16 (11.8)
Grade 3 or 4	0	2 (2.2)	3 (2.7)	3 (2.2)
Grade 3	0	2 (2.2)	3 (2.7)	3 (2.2)
Grade 4	0	0	0	0
Neutrophil count decreased, m^a	65	93	113	136
Any Grade	5 (7.7)	5 (5.4)	7 (6.2)	14 (10.3)
Grade 3 or 4	1 (1.5)	1 (1.1)	2 (1.8)	4 (2.9)
Grade 3	1 (1.5)	1 (1.1)	1 (0.9)	3 (2.2)
Grade 4	0	0	1 (0.9)	1 (0.7)

Any Grade = the number of subjects with an increase of at least 1 CTCAE grade from baseline to the worst postbaseline value of any grade. Grade 3, Grade 4 = the number of subjects with an increase of at least 1 CTCAE grade from baseline to the worst postbaseline value that is Grade 3 or 4. Laboratory Results were graded using CTCAE version 5.0.

CTCAE = Common Terminology Criteria for Adverse Events, CTCL= cutaneous T-cell lymphoma, PTCL = peripheral T-cell lymphoma.

A: Indicates the number of subjects with nonmissing baseline and at least 1 postbaseline result in the relevant safety set; this number was used to calculate percentages within each laboratory test.

Clinical Chemistry

In the Study 302 Stage I-III Safety Set, there were notable trends over time in the clinical chemistry parameters of increased ALT, increased AST, and decreased albumin.

These laboratory abnormalities occurred mostly in Cycles 1 and 2. On Cycle 1 Day 8, increased ALT values of Grades 1, 2, and 3 were observed in 27 (42.9%), 5 (7.9%), and 8 (12.7%) subjects, respectively, with no Grade 4 values. By Cycle 2 Day 8, the incidence had decreased substantially when increased ALT values of Grades 1, 2, and 3 were observed in 17 (28.8%), 0, and 1 (1.7%) subject, respectively. A similar pattern was observed for increased AST.

On Cycle 1 Day 8, Grades 1 and 2 decreased albumin values were observed in 13 (20.6%) and 6

(9.5%) subjects, respectively, with no values of Grade 3 or higher. The incidence of abnormal values significantly decreased after that, with only 2 (3.4%) subjects having a Grade 1 value on Cycle 2 Day 8 and no values of Grade 2 or higher.

The overall pattern of chemistry abnormalities was similar across the safety sets with the exception of the incidences of Grade 3 increased ALT and increased AST that were higher in the All Study/All Stage CTCL and All CTCL/PTCL Safety Sets relative to the Study 302 Stage I-III Safety Set (increased ALT, 22.4% and 28.1%, respectively, versus 13.4%; increased AST, 8.6% and 15.8%, respectively, versus 4.5% (Table 33). Of note, there were no Grade 3 or Grade 4 abnormalities of increased creatinine or decreased sodium levels.

Table 33: Clinical Chemistry Laboratory Abnormalities

Clinical Chemistry Parameter Worst Postbaseline Grade	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
ALT increased, m^a	67	96	116	139
Any Grade	44 (65.7)	62 (64.6)	81 (69.8)	102 (73.4)
Grade 3 or 4	9 (13.4)	13 (13.5)	26 (22.4)	40 (28.8)
Grade 3	9 (13.4)	13 (13.5)	26 (22.4)	39 (28.1)
Grade 4	0	0	0	1 (0.7)
AST increased, m^a	67	96	116	139
Any Grade	40 (59.7)	55 (57.3)	74 (63.8)	97 (69.8)
Grade 3 or 4	3 (4.5)	3 (3.1)	10 (8.6)	23 (16.5)
Grade 3	3 (4.5)	3 (3.1)	10 (8.6)	22 (15.8)
Grade 4	0	0	0	1 (0.7)
Alkaline Phosphatase increased, m^a	67	96	116	139
Any Grade	12 (17.9)	17 (17.7)	23 (19.8)	32 (23.0)
Grade 3 or 4	0	1 (1.0)	1 (0.9)	1 (0.7)
Grade 3	0	1 (1.0)	1 (0.9)	1 (0.7)
Grade 4	0	0	0	0
Total Bilirubin increased, m^a	66	95	115	138
Any Grade	2 (3.0)	4 (4.2)	6 (5.2)	8 (5.8)
Grade 3 or 4	0	1 (1.1)	1 (0.9)	1 (0.7)
Grade 3	0	1 (1.1)	1 (0.9)	1 (0.7)
Grade 4	0	0	0	0
Albumin decreased, m^a	67	96	117	140
Any Grade	29 (43.3)	44 (45.8)	62 (53.0)	79 (56.4)
Grade 3 or 4	1 (1.5)	1 (1.0)	2 (1.7)	3 (2.1)
Grade 3	1 (1.5)	1 (1.0)	2 (1.7)	3 (2.1)
Grade 4	0	0	0	0

Clinical Chemistry Parameter Worst Postbaseline Grade	Study 302 Stage I-III (N=69) n (%)	Study 302 Stage I-IV (N=98) n (%)	All Study/ All Stage CTCL (N=119) n (%)	All CTCL/PTCL (N=142) n (%)
CPK increased, m^a	36	45	52	59
Any Grade	8 (22.2)	8 (17.8)	9 (17.3)	10 (16.9)
Grade 3 or 4	1 (2.8)	1 (2.2)	1 (1.9)	1 (1.7)
Grade 3	0	0	0	0
Grade 4	1 (2.8)	1 (2.2)	1 (1.9)	1 (1.7)

Any Grade = the number of subjects with an increase of at least 1 CTCAE grade from baseline to the worst postbaseline value of any grade. Grade 3, Grade 4 = the number of subjects with an increase of at least 1 CTCAE grade from baseline to the worst postbaseline value that is Grade 3 or 4. Laboratory Results were graded using CTCAE version 5.0.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CPK = creatine phosphokinase, CTCAE = Common Terminology Criteria for Adverse Events, CTCL= cutaneous T-cell lymphoma, PTCL = peripheral T-cell lymphoma.

a: Indicates the number of subjects with nonmissing baseline and at least 1 postbaseline result in the relevant safety set; this number was used to calculate percentages within each laboratory test.

In all ONTAK-treated subjects, the highest frequency of worst post-baseline Grade $\geq$ 3 lab abnormality was increased ALT, reported in 29.3% of subjects.

The Applicant's Position:

Laboratory findings for E7777 were consistent across the E7777 safety datasets and with the ONTAK Study 11 safety profile.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment and the lab-shift data presented above. Analysis of lab-shift data was used for laboratory reporting in the USPI.

Vital Signs

Data:

Decreases in blood pressure were of clinical interest because of the potential occurrence of hypotension with CLS and infusion reactions. In the Study 302 Stage I-III Safety Set, more than half the subjects had at least some decrease in systolic or diastolic blood pressure (SBP or DBP), with postbaseline SBP value of < 90 mmHg or a postbaseline DBP value of < 60 mmHg being reported for 13.0% and 72.5% of subjects, respectively. The clinical value of DBP <60 mm Hg in the absence of concomitant SBP <90 mm Hg is uncertain. Most decreases in blood pressure occurred around Day 2 or Day 3 of each cycle, and returned to baseline levels by Day 8. These results were similar across the safety sets.

In ONTAK Study 11, TEAEs of hypotension were reported in 12.0% of ONTAK-treated subjects. The incidence of moderately severe (equivalent to Grade 3) hypotension was 6.0%, and there were no reports of severe (equivalent to Grade 4) hypotension.

The Applicant's Position:

Vital signs findings for E7777 were consistent across the E7777 safety datasets and with the ONTAK Study 11 safety profile.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that hypotension is a known risk in the setting of CLS and infusion-related reactions. The risk of CLS and infusion-related reactions are included in the USPI as a boxed warning and a warning and precaution, respectively.

Electrocardiograms (ECGs)

Data:

Shifts in ECG findings from normal at Baseline to abnormal (including abnormal not clinically significant) postbaseline were seen in 32.3% of subjects in the Study 302 Stage I-III Safety Set; few were reported as TEAEs. These findings were comparable across the safety sets. Shifts in ECG findings were not reported in ONTAK clinical studies.

The Applicant's Position:

ECG findings for E7777 were consistent across the E7777 safety datasets.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

QT

Data:

The incidence of Grade ≥ 3 QTcF prolongation (QTcF > 500 ms; n=65), identified by analysis of ECG results, was 4.6% (3 subjects). No TEAE of Torsade de pointes, sudden death, or ventricular arrhythmia was reported in association with these ECG abnormalities. Postbaseline increase in QTcF from Baseline of >30 msec or >60 msec was observed in 15 (23.1%) and 2 (3.1%) subjects, respectively. The reported incidence of TEAE (i.e., clinical AE) of prolonged ECG QT was low at 4.3% (3 subjects; all Grade 1). These findings were similar across the safety sets. No QTc analyses were performed in ONTAK clinical studies.

The Applicant's Position:

QT findings for E7777 were consistent across the E7777 safety datasets.

The FDA's Assessment:

The FDA agrees with the Applicant's position, and notes that across all safety populations there was no signals for arrhythmias secondary to QT prolongation.

Immunogenicity

Data:

Immunogenicity

The immunogenicity of E7777 has been evaluated using two electrochemiluminescence-based immunoassays for the detection of antibodies against E7777 and IL-2 domain and two cell-based assays for detection of neutralizing antibodies.

In Study 302, among patients with any stage CTCL who received E7777 9 µg/kg/day,

- 78.0% (71/91) of subjects had pre-existing antibodies to E7777 due to the widespread vaccination against DT and 7.8% (7/91) of subjects had neutralizing anti-E7777 antibodies. Among these subjects with pre-existing antibodies, 5.5% (5/91) of the subjects had antibodies against IL-2 but none had neutralizing antibodies against IL-2.
- After treatment with E7777, 92.9% (78/84) and 82.1% (69/84) of subjects developed antibodies against E7777 and IL-2, respectively.
- Neutralizing antibodies to the IL-2 domain of E7777 were detected in 11.6% (8/69) of subjects.
- Treatment with E7777 led to an increase in the titers. The median anti-E7777 antibody titers in subjects with treatment-emergent antibodies were 151, 181, 84, and 59 times higher than baseline at Day 1 of Cycle 2, Cycle 3, Cycle 5, and Cycle 8, respectively. The anti-IL-2 antibody titers were 2, 49, 437, and 1312 times higher than baseline at these same visits, respectively.

Anti-Drug Antibody Effects on Safety

The observed incidence of any TEAEs was generally lower in anti-E7777 or anti-IL-2 antibody-positive subjects except for visual impairment and rash. The incidence of CLS in Study 302 was lower in anti-E7777 antibody-positive subjects (21.8% [17/78]) compared with anti-E7777 antibody-negative subjects (83.3% [5/6]). Similarly, it was lower in anti-IL-2 antibody-positive subjects (19.1% [13/68]) compared with anti-IL-2 antibody-negative subjects (60.0% [9/15]).

The presence of either anti-E7777 or anti-IL-2 antibodies did not appear to adversely impact the safety profile of E7777.

The Applicant's Position:

The presence of either anti-E7777 or anti-IL-2 antibodies did not appear to adversely impact the safety profile of E7777. Immunogenicity findings for E7777 were consistent with the immunogenicity profile of ONTAK.

The FDA's Assessment:

Refer to Section 6 for the FDA Clinical Pharmacology review of the immunogenicity profile of E7777.

8.2.5. Analysis of Submission-Specific Safety Issues

Data:

TEAEs deaths, SAEs, treatment-related SAEs, treatment discontinuations due to TEAEs, dose modifications (drug interruption or dose reduction) due to TEAEs, AESIs are described in prior sections of this document. There were no severe (CTCAE Grade ≥ 3) or serious AEs of visual impairment.

The Applicant's Position:

There are no other submission-specific safety issues.

The FDA's Assessment:

Specific AESIs warranting additional exploration and select laboratory findings are discussed in the "Adverse Events of Special Interest" and "Laboratory Findings" sections above.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data and The Applicant's Position:

Patient-reported outcomes are presented in Section 8.1.2.

The FDA's Assessment:

The patient-reported outcomes (PRO) data were considered as supportive data for this application. Health-related QoL assessments were performed at baseline, Day 1 of each subsequent cycle during the treatment period, at EOT, and during every tumor assessment visit during the Follow-up Period. The FDA acknowledges the descriptive improvements in PROs, however, it is difficult to ascertain if the improvements in PROs translate to clinically meaningful benefit. Additionally, the single-arm, open-label trial design limits the PRO data interpretations since a patient's knowledge of treatment regimen may lead to systematic overestimation or underestimation of treatment effect.

8.2.7. Safety Analyses by Demographic Subgroups

Data and The Applicant's Position:

Female and male subjects, elderly patients, and different racial groups were well-represented in the safety analysis sets. Analyses of TEAEs based on age, sex, race, and CTCL disease stage at study entry were performed. No clinically relevant differences were observed in the subgroup analyses that warrant dose-adjustment or special precautions.

No safety concerns were identified by review of safety data by demographic subgroup.

The FDA's Assessment:

The FDA agrees with the Applicant's position that descriptively, there are no clinically relevant differences in safety based on age, sex, race, and CTCL stage. However, these analyses are limited by small sample size and should be interpreted with caution

8.2.8. Specific Safety Studies/Clinical Trials

Data and The Applicant's Position:

Not applicable. No specific safety studies were conducted to support this BLA.

The FDA's Assessment:

Not Applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data and The Applicant's Position:

Not applicable. Carcinogenicity studies have not been conducted with E7777.

The FDA's Assessment:

Not Applicable.

Human Reproduction and Pregnancy

Data and The Applicant's Position:

There were no reports of pregnancy in female subjects or in female partners of male subjects receiving E7777 in the clinical trial program. There are no adequate data on the developmental risks associated with use of E7777 in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with E7777. CTCL is typically a disease of an older population as evidenced by the population of Study 302 where the median age was 64 years, nevertheless, women of childbearing potential may be eligible for treatment. Based on its mechanism of action, E7777 may cause fetal harm when administered to a pregnant woman. Therefore, pregnant women should be advised of the potential risk to a fetus.

The FDA's Assessment:

The FDA agrees with the Applicant's statement. The USPI includes a Warning and Precaution on embryo-fetal toxicity.

Pediatrics and Assessment of Effects on Growth

Data and The Applicant's Position:

No clinical studies of E7777 have been conducted or are currently planned in pediatric populations. Pediatric CTCL is rare and usually presents as early stage disease. In most cases,

skin-directed therapies (e.g., topical therapies or phototherapy) result in complete response. E7777 is unlikely to represent a meaningful therapeutic benefit over existing skin-directed therapies for pediatric patients or to be used by a substantial number of pediatric patients. The Agency agreed (Ref ID 110489) that, due to the rarity of pediatric CTCL (specifically patients who require systemic therapy), it would be impracticable to evaluate a sufficient number of pediatric patients with CTCL in a clinical study with E7777.

The FDA's Assessment:

The FDA agrees with the Applicant's statement.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data and The Applicant's Position:

The highest dose of E7777 evaluated in clinical studies was 15 µg/kg. There is no experience with higher doses or deliberate or accidental overdose.

There is no reason to expect drug abuse of E7777 as it is administered IV in a clinic setting. There are no data available regarding withdrawal or rebound effects related to E7777; in clinical studies, subjects post-treatment follow up was conducted 30 or 37 days after their last dose. No formal studies have been conducted to assess withdrawal and rebound effects from treatment with E7777.

The FDA's Assessment:

The FDA agrees with the Applicant's statement.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

E7777 (Remitoro) was approved in Japan for the treatment of relapsed or refractory PTCL or CTCL in March, 2021. As of 31 Mar 2022, the estimated total number of patients exposed to Remitoro was (b) (4), including 43 subjects from the ongoing postmarketing observational study E7777-M081-501 (NCT05137847) and (b) (4) patients treated in the community. A total of 41 SAEs among 25 postmarketing patients were reported as of 17 Mar 2022. Of these, a total of 8 SAEs among 4 CTCL patients were considered related to Remitoro by the reporter: CLS (n=3) and 1 report each of abnormal hepatic function, pneumonia, pyrexia, rhabdomyolysis, and sepsis. The most common SAEs, regardless of causality, were CLS, pyrexia, malignant neoplasm progression, cytomegalovirus infection, and abnormal hepatic function.

The Applicant's Position:

The postmarketing SAEs were consistent with the clinical study safety profile of E7777 in subjects with CTCL. No new safety concerns have been identified from postmarketing experience.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

Data and The Applicant's Position:

The safety profile of E7777 as demonstrated in the clinical trial program, and postmarketing data from Japan is consistent with the ONTAK Study 11 safety profile, with no new safety signals or unexpected safety findings. Potential new safety concerns are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected AEs.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

Data:

Across all 3 studies of E7777, the most common AEs ($\geq 20\%$) in subjects with CTCL (N=119) were nausea, ALT increased, AST increased, hypoalbuminemia, fatigue, chills, peripheral edema, constipation, pyrexia, and CLS. The most common SAEs ($\geq 5\%$) were CLS (12.6%) and infusion reactions (6.7%). Treatment was discontinued in 15.1% (18/119) of patients due to adverse reactions.

AESI: Clinically, the most important AESIs are CLS, infusion reactions, visual impairment, and hepatotoxicity. There were no severe (Grade ≥ 3) or serious AEs of visual impairment reported with E7777. Other AESIs are hypersensitivity, rash, infection, and thrombotic events.

In the Study 302 Stage I-III Safety Set, the number of TEAEs by cycle peaked in Cycles 1 and 2, then rapidly decreased and remained low thereafter. Similar time-related trends were seen in TEAEs of Grade 3 or higher, SAEs, and treatment-related TEAEs.

Examination of immunogenicity and AEs showed no evidence of a clinically meaningful impact of treatment-emergent ADAs on safety measures.

The Applicant's Position:

Analysis of the safety profile of E7777 9 $\mu\text{g}/\text{kg}$ for the treatment of patients with persistent or recurrent CTCL showed an acceptable safety and tolerability profile that was consistent across Studies 302, 205 and 101. The safety profile of E7777 was manageable, as shown by the low rate of study drug discontinuations due to AEs. The safety profile was consistent with the ONTAK Study 11 safety profile, with no new safety signals or unexpected findings observed.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position. The safety data support that E7777 demonstrated an acceptable safety profile in patients with relapsed or refractory CTCL.

The safety profile of E7777 was primarily supported by the evaluation of 119 patients with R/R CTCL that received the recommended dose and regimen. The median duration of treatment was 12.7 cycles (range 0.1 to 126.1), with 75% exposed for 8 cycles. The most common adverse events ($\geq 20\%$) were transaminase elevation, nausea, edema, fatigue, hypoalbuminemia, musculoskeletal pain, rash, chills, constipation, fever, and capillary leak syndrome. The most common Grade 3 to 4 laboratory abnormalities ($\geq 10\%$) were ALT increased and lymphocyte count decreased. Serious adverse events occurred in 37.8%, most often due to capillary leak syndrome and infusion-related reaction. Adverse events leading to treatment interruption occurred in 32.8% most often due to capillary leak syndrome. Adverse events leading to treatment discontinuation occurred in 15.1%, most often due to capillary leak syndrome and mental status changes. Overall, the primary safety issues identified with E7777 include CLS, visual impairment, infusion related reaction and hepatotoxicity.

Based on the FDA's evaluation of the data, the USPI will need to include a Boxed Warning for CLS and Warning & Precaution sections for visual impairment, infusion-related reactions and hepatotoxicity.

The Applicant submitted a 120-safety update on December 23, 2022. Based on data cutoff, there were 3 fatal events from the Japanese post-marketing study. One patient with angioimmunoblastic T-cell lymphoma experienced CLS and hepatic function disorder and died 9 days after commencing denileukin diftitox. The risk of CLS and hepatotoxicity is included in labeling. Two additional patients on this study had pneumonia (including aspiration pneumonia) leading to a fatal outcome. No new safety signals were identified.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

Efficacy

The efficacy of E7777 is based primarily on the results from E7777-G000-302, a single-arm, multicenter trial in patients with relapsed or refractory cutaneous T cell lymphoma. Sixty-nine patients with Stage I-III CTCL who previously received 1 prior systemic therapy and received denileukin diftitox at the recommended dosage were the primary efficacy population. The efficacy was supported by studies E7777-J081-205 and E7777-J081-101, open-label, single-country phase 2 and Phase 1/1b trials respectively that included a total of 21 Japanese patients with R/R CTCL.

Efficacy was established on the basis of overall response rate according to ISCL/EORTC Global Response Score (GRS) per Independent Review Committee (Olsen 2011) in Study 302. Among the 69 patients with Stage I-III CTCL, the ORR per IRC was 36% (95% CI: 25, 49), with 9% achieving best response of CR. With a median follow-up for DOR of 6.5 months, there were 13 patients (52%, 13/25) with a duration $\geq$ 6 months and 5 patients (20%, 5/25) with a duration $\geq$ 12 months.

Efficacy was supported by Study 205 and 101, which enrolled patients with similar baseline disease characteristics, although the difference in location of enrollment limits the comparability of the efficacy results. Nevertheless, the ORR appeared to be similar in the CTCL patients from the three studies.

Given that the three studies, -302, -205, and -101 were open-label and single-arm studies, there are inherent limitations in interpreting the study data and Applicant's analyses results. For example

- Analyses for time-to-event endpoints are not interpretable in a single arm study due to lack of comparator arm. FDA considers such endpoints exploratory and not adequate to be used as measures of efficacy in single-arm trials intended to support approval.
- A 25% ORR rate was chosen to compare with ORR rates obtained in Study 302. The use of this 25% control rate from historical trials to assess whether the observed treatment effect represents an improvement over available therapy is challenging. There can be differences across trials (e.g., in design, conduct, response assessment intervals, study population, etc.) which may or may not be easily discernible and which could lead to erroneous conclusions regarding observed differences in the response estimate between the investigational arm and a historical control (e.g., erroneously attributing differences in response rate to the investigational drug). Thus, the null hypothesis of 25% was only used to inform the sample size for Study 302.

8.4 Conclusions and Recommendations

The FDA's Assessment:

Substantial evidence of efficacy of denileukin diftitox in patients with relapsed or refractory Stage I-III CTCL is based on overall response rate in Study 302, a single-arm, multicenter trial of denileukin diftitox in patients with CTCL. Sixty-nine patients with Stage I-III CTCL who previously received 1 prior systemic therapy and received denileukin diftitox at the recommended dosage were evaluable for efficacy. The ORR per IRC was 36.2% (95% CI: 25.0, 48.7) and the CR and PR rate was 9% and 27% respectively, according to the Olsen (2011) Criteria. The median time to response was 1.4 months (range: 0.7 to 5.6 months). The median (95% CI) DOR using Kaplan-Meier (KM) estimate was not estimable (NE) among the 25 responders due to censoring. In the

25 patients who achieved a response, the duration of response exceeded 6 months in 52% (13/25) and 12 months in 20% (5/25). Among responders, the median follow-up for DOR was 6.5 months (range: 3.0+, 23.5+ months). The efficacy data including response rates and durability of response support the determination of substantial evidence of effectiveness with denileukin diftitox.

The safety profile was deemed acceptable. The safety of denileukin diftitox was evaluated in 119 patients with relapsed or refractory Stage I-IV CTCL across three clinical trials. Patients received treatment with denileukin diftitox 9 mcg/kg daily from Day 1 through Day 5 of each 21-day cycle. Treatment was administered until disease progression or unacceptable toxicity. The median number of cycles was 5 (range: 1 to 42), with 13% exposed for 6 months or longer. Serious adverse events (SAEs) occurred in 38% of patients, most often from capillary leak syndrome, infusion-related reaction, or sepsis. Adverse events (AEs) leading to treatment discontinuation occurred in 15% of patients, treatment interruption in 33%, and dose reductions in 4%. The most common reasons for treatment modification was capillary leak syndrome and infusion-related reaction. A fatal AE of capillary leak syndrome occurred in 1 patient. The most common ($\geq 20\%$) adverse events, including laboratory abnormalities, were increased transaminases (70%), albumin decreased (53%), nausea (40%), edema (35%), hemoglobin decreased (34%), fatigue (30%), musculoskeletal pain (26%), rash (23%), chills (22%), constipation (22%), pyrexia (21%), and capillary leak syndrome (20%).

Benefit-Risk: Based on ORR and durability, denileukin diftitox has demonstrated meaningful clinical activity in the Stage I-III CTCL population, along with an acceptable safety profile to support the following indication:

- The treatment of patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

The overall benefit-risk, however, is not favorable for denileukin diftitox due to deficiencies related to the product quality. See Section 4.2 for further information. Thus, the FDA review team recommends a complete response for this application.

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The application was not presented to the Oncologic Drug Advisory Committee or other external consultants, as it did not raise significant efficacy or safety concerns for the proposed indication.

10 Pediatrics

The Applicant's Position:

In accordance with 505B(a)(5)(A), the Applicant requests a full waiver for the required pediatric assessments or reports on the targeted pediatric cancer investigation for the indication outlined and described in the Agreed Initial Pediatric Study Plan (Received on 24 Jan 2022 from FDA; Ref ID 4925830) for E7777 for the treatment of persistent or recurrent CTCL (b) (4)

Pediatric Age Groups	Indication	Reason for Waiver
0 to <17 years	Treatment of persistent or recurrent CTCL (b) (4) (claimed indication in adults)	Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used by a substantial number of pediatric patients, as relapsed or refractory CTCL, requiring systemic therapy rarely occurs in pediatric patients.

The FDA's Assessment:

The FDA agrees with the Applicant's position. A pediatric population was not included in any of the studies contained in this application. Efficacy is not established in the pediatric population.

11 Labeling Recommendations

Data and The Applicant's Position:

This is an original application. The Applicant's proposed label is provided in Module 1.14.1.2.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Highlights	N/A	FDA modified the established therapeutic class (EPC) from "^{(b) (4)}" to "IL2-receptor-directed cytotoxin". FDA modified the boxed warning to include ^{(b) (4)} capillary leak syndrome.
1 Indications and Usage	BRAND NAME is indicated for the treatment of adult patients with persistent or recurrent cutaneous T-cell lymphoma after at least one prior systemic therapy, ^{(b) (4)}	FDA modified this section to reflect the data supporting efficacy; the indication has been revised to: LYMPHIR is indicated for the treatment of adult patients with relapsed or refractory stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.
2 Dosage and Administration	Dosage modifications are provided for potential adverse reactions; premedication information is included; instructions for preparation (dilution) and administration via intravenous infusion (consistent with regulations and Guidances) are provided.	FDA modified this section to include a new subsection 2.1 Important Dosing Information to inform prescribers that, prior to starting each cycle hepatic and renal function should be assessed and serum albumin should be at least 3 g/dL. A new subsection 2.3 Recommended Premedications added to include recommendations for premedications to reduce the risk

		of infusion-related reactions. Section 2.4 Dosage Modifications for Adverse Reactions was modified to add clarity to the dosage modifications table and to add a new table for instructions for restarting Lymphir after a dosage delay due to toxicity. Section 2.5 Preparation and Administration was modified to align with current labeling practice and to provide added clarity.
5 Warnings and Precautions (W&P)	Data from clinical trials and management guidelines for infusion reactions, capillary leak syndrome, and visual (b) (4) are included.	FDA modified this section to reorder the W&P as follows: capillary leak syndrome 5.1, visual impairment (b) (4) (b) (4) 5.2, and infusion-related reactions 5.3. The visual impairment W&P was modified to include recommendations to perform baseline ophthalmic examination and monitoring as clinically indicated. A new W&P 5.4 was added for hepatotoxicity, based on the pooled safety population, due to ALT/AST elevations of 70% overall, with grade 3 or 4 of 22%.
6 Adverse Reactions	Summary text based on 3 clinical trials and specific data from the pivotal trial are provided. Common ADR and laboratory abnormalities tables (pivotal trial) are included.	FDA modified this section to include a pooled safety population statement at the beginning of section 6.1 including 119 patients from 3 clinical trials described in Warnings and

		Precautions section 5. FDA limited the remainder of section 6.1 to the 69 patients with relapsed or refractory stage I-III CTCL in study E7777-G000-302 Edits made to align with current labeling practice and recommendations in guidance and regulations.
8 Use in Specific Populations	Sections 8.1 and 8.2 proposed content is consistent with Pregnancy and Lactation Labeling Rule (PLLR). Section 8.3 provides specific contraception instructions for females.	FDA modified this section as follows: In section 8.1, information was added to communicate the nature of the risk based on denileukin diftitox’s mechanism of action. In section 8.3, revisions to align with current labeling practice were made and information on the potential risk to male infertility was added based on findings from a 14-week toxicology study in rats. In section 8.5, geriatric use information was added for the 69 patients in the efficacy population to align with recommendations in the <i>Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry</i>.
12 Clinical Pharmacology	Details provided on mechanism of action, pharmacodynamics, pharmacokinetics, and immunogenicity.	FDA modified this section to align with current labeling guidances and practice.

		FDA revised section 12.1 Mechanism of Action to remove (b) (4) FDA modified section 12.2 Pharmacodynamics to add the statement that the time course of pharmacodynamic response for denileukin diftitox is unknown as per 21 CFR 201.57(c)(13)(i)(B). FDA modified section 12.3 Pharmacokinetics (PK) to limit discussion of PK to the recommended dosage of 9 mcg/kg/day. FDA modified section 12.6 Immunogenicity to align with recommendations in guidance.
14 Clinical Studies	Includes description of studies: • Study 302 (NCT01871727; pivotal Phase 3) design and patient population, response rates (overall, complete, and partial), duration of response, and time to response. • (b) (4)	FDA modified this section to limit the discussion of efficacy to the indicated population of relapsed or refractory stage I to IV CTCL from study E7777-G000-302. FDA removed all information for (b) (4)

The FDA's Assessment:

FDA modified sections of the USPI as described in the table above.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team does not recommend a REMS. Based on the observed safety profile of

E7777, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The review team recommends one postmarketing requirements (PMR), which aims to address the need for additional data to characterize ophthalmologic toxicity in patients receiving E7777 and inform patient labeling regarding risk, recommended assessments and mitigation strategies.

Postmarketing requirements:

1. Conduct a clinical trial to further characterize the known serious risk of visual impairment including risk factors, manifestations, and outcomes in patients with cutaneous T-cell lymphoma treated with denileukin diftitox-cxd. The visual impairment monitoring procedures in this study should include, but should not be limited to, visual acuity, slit lamp examination, dilated funduscopy examination, and optical coherence tomography. The study will ascertain and closely monitor any potential risk factors associated with visual impairment. Include data on at least 50 patients with visual impairment.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1 References

The Applicant's References:

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The FDA's References:

The FDA had no additional references to add.

19.2 Financial Disclosure

The Applicant's Position:

159

Version date: January 2020 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

No clinical investigators in Study 302 (Lead-In part and Main Study) had significant disclosable financial arrangements (i.e., none >\$25,0000).

Eight clinical investigators in Study 205 had significant disclosable financial arrangements (i.e., >\$25,0000). To minimize potential bias, the Sponsor implemented the same measures across all study sites:

- The primary efficacy analysis of ORR was determined by the independent ESEC.
- Central review was conducted by the Imaging Review Committee for nodal and extranodal lesions. In addition, overall responses and BOR was determined by the ESEC based on the nodal and extranodal lesions reviewed by the Imaging Review Committee and responses on liver/spleen enlargement, bone marrow infiltration, skin lesion, and peripheral blood disease evaluated by the investigator or subinvestigator.

• Secondary endpoints (except OS) were also judged by the ESEC: PFS , DOR, TTR and CRR. The Applicant believes these measures are adequate to minimize potential bias in the study including for those investigators with disclosable financial interests/arrangements.

A list of all investigators from Study 302 and from Study 205 can be found in Module 1.3.4 Financial Certification and Disclosure documents.

The FDA's Assessment:

The FDA agrees with the Applicant's statement and tables below.

Covered Clinical Study (Name and/or Number):* E7777-G000-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>232</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details	Yes ☐	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* E7777-J081-205

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>320</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>8</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>8</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3 Nonclinical Pharmacology/Toxicology

Data and The Applicant's Position:

Not applicable. Nonclinical pharmacology and toxicology data are presented in Section 5.

The FDA's Assessment:

FDA concurs.

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

The FDA's Assessment:

E7777 concentration in human serum samples from E7777-G000-302, E7777-J081-205, and E7777-J081-101 were quantified using a bioanalytical method as summarized in Table 34 and Table 35 below.

Table 34: Bioanalytical Method Validation Summary for E7777 Quantification for Studies E7777-G000-302 and E7777-J081-205

Bioanalytical method validation report name, amendments	Method: ICD 370 v 3.0 Validation of an Electrochemiluminescent Method for the Quantitation of E7777 in Human Serum (Reports: RCQG5, RCQG3 Addendum 1 – long term storage, and RCQG7 Addendum 2 – selectivity/specificity)	
Method description	The calibration standards, QC, blank and study samples were first diluted in an acid dissociation buffer, then neutralized, and incubated with biotinylated anti-IL-2 antibodies and ruthenium-labeled anti-DT (D5A7) antibodies allowing E7777 to form complexes with labeled antibodies. The complexes were added to streptavidin-coated multi-array 96-well plates and the plates were washed and read using qualified MSD SECTOR Imager plate readers.	
Materials used for calibration and QC	E7777 (Lot No: RM-IP-001, 171 µg/mL)	
Validated assay range	5.00 to 3000 ng/mL (Range with acceptable selectivity is 10.0-3000 ng/mL)	
Minimum required dilutions (MRDs)	1:26	
Regression model & weighting	4-PL, 1/Y ²	
Validation parameters	Method validation summary	
Calibration curve performance during accuracy & precision	Number of non-zero standard calibrators from LLOQ to ULOQ: 5, 10, 25, 62.5, 125, 300, 750, 1500, 2500, and 3000 ng/mL	>6
	Cumulative accuracy (%bias)	-3.70 to 4.31%
	Cumulative precision (%CV)	≤ 3%
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 7 QCs: QCs levels: 10 (LLOQ), 15 (LQC), 300, 2250 (HQC), 2500, 3000 (ULOQ) ng/mL	-11.2 to 2.81%
	Inter-batch %CV	≤ 10%

NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)

	Percent total error (TE)	≤ 14.8%
Selectivity & matrix effect	Tested with 10 lots each from individual healthy donors and T-cell lymphoma patients. Individual serum samples were spiked with E7777 at LLOQ and HQC levels. Ranges of observed bias from nominal concentrations are: • LLQC in healthy individuals: -16.1 to 6.24% • HQC in healthy individuals: -2.87 to 8.01% • LLQC in patients: -24.9 to 6.62% • HQC in patients: 3.03 to 14.1% No matrix effect observed. However, ADA titer values from these individuals have not been reported.	
Hemolysis effect	No effect from hemolyzed matrix was observed when samples containing 5% fully lysed whole blood were tested at blank, LQC and HQC.	
Lipemic effect	No effect from lipemic samples observed when tested at blank, LQC and HQC.	
Interference & specificity	The ability of endogenous ADAs to impact the quantification of E7777 was evaluated using 13 ADA positive incurred samples spiked at 15 and 225 ng/mL of E7777. The presence of moderate to high levels of ADAs may affect the ability of this method to accurately quantify E7777 when the titers are high.	
Dilution linearity & hook effect	Highest concentration tested at 17.1 mcg/mL and at dilution factors 8, 16 and 100. Range of observed bias were -10.5 to 7.47%.	
Bench-top/process stability	Stable up to 8 hours at room temperatures. Stability was assessed using LQC and HQC and the observed %bias ranged from -8.06 to 12.0% of nominal concentrations	
Freeze-Thaw stability	Stable up to 3 cycles. Stability was assessed using LQC and HQC and the observed %bias ranged from -4.03 to 17.9% of nominal concentrations	
Long-term storage	Stability was assessed using LQC and HQC up to 366 days at 25±5°C and 1107 days at 80±10°C	
Parallelism	Not applicable	
Method performance in clinical study E7777-G000-302: (Sample testing report ID: RAOQ2)		
Assay passing rate	87% (46 out of 53 runs including ISR)	
Standard curve performance	Cumulative bias range: -3.93 to 3.00% Cumulative precision: ≤7.03% CV	
QC performance	Cumulative bias range: 3.00 to 4.86% Cumulative precision: ≤17.3% CV TE: ≤25%	
Method reproducibility	Incurred sample reanalysis was performed in 11.6% of study samples and 97 % of samples met the pre-specified criteria	
Study sample analysis/ stability	1040 original and 988 back-up samples were received frozen at bioanalytical site in good condition from RAOQ2. The samples were stored frozen at (b)(4) within established storage duration except at the time for analyses	
Method performance in clinical study E7777-J081-205: (Sample testing report ID: RFPT)		
Assay passing rate	73% (17 out of 23 runs including ISR)	
Standard curve performance	Cumulative bias range: -2.88 to 3.41% Cumulative precision: ≤2.62% CV	
QC performance	Cumulative bias range: -1.12 to 5.43% Cumulative precision: ≤8.45% CV TE: ≤13.9%	
Method reproducibility	Incurred sample reanalysis was performed in 11% of study samples and 97.4 % of samples met the pre-specified criteria	

Study sample analysis/ stability	338 human serum samples were received frozen and in good condition from (b) (4) between 02 Nov 2016 and 25 Apr 2019 and stored frozen at (b) (4) and stored frozen at (b) (4) within established storage duration except at the time for sample analyses

Table 35: Bioanalytical Method Validation Summary for E7777 Quantification for Study E7777-J081-101

Bioanalytical method validation report name, amendments	Method: ICD 370 v 1.0 Validation of an Electrochemiluminescent Method for the Quantitation of E7777 in Human Serum (Reports: AOW2, Addendum 1 – long term storage and Addendum 2)	
Method description	The calibration standards, QC, blank, and study samples were first diluted in PBS followed by an addition of acid dissociation buffer and incubated with biotinylated anti-IL-2 antibodies and ruthenium-labeled anti-DT (D5A7) antibodies allowing E7777 to form complexes with labeled antibodies. The samples were added to streptavidin-coated multi-array 96-well plates and the plates were washed and read using qualified MSD SECTOR Imager plate readers.	
Materials used for calibration curve	E7777 (Lot No: DEV-PI-ENG, 175 µg/mL)	
Validated assay range	30.0 to 3000 ng/mL	
Minimum required dilutions (MRDs)	1:15 in PBS followed by 1:10 in acid dissociation buffer	
Regression model & weighting	5-PL, 1/Y ²	
Validation parameters	Method validation summary	
Calibration curve performance during accuracy & precision	Number of non-zero standard calibrators from LLOQ to ULOQ: 5 (Anchor point), 10, 15, 20, 50, 100, 200, 1000, 2000, and 3000 ng/mL	6
	Cumulative accuracy (%bias)	-13.8 to 6.64%
	Cumulative precision (%CV)	≤12.4%
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 7 QCs QCs levels: 10, 15, 30, 250, 1800, 2000, and 3000	-3.44 to 6.31%
	Inter-batch %CV	≤ 18.6%
	Percent total error (TE)	≤ 21% (in 10 ng/mL)
Selectivity & matrix effect	Tested with 10 lots each from individual healthy donors and T-cell lymphoma patients. Individual serum samples were spiked with E7777 at LLOQ and HQC levels. Ranges of observed bias from nominal concentrations are: 30 ng/mL in healthy individuals: -70.6 to 78% 90 ng/mL in healthy individuals: -2.87 to 8.01% 30 ng/mL in patients: 3.36 to 46.1% 90 ng/mL in patients: -15.4 to -3.8% 400 ng/mL in patients: -5.24 to 13.1% A matrix effect was observed likely due to pre-existing anti-diphtheria. The selectivity was within the acceptable range when the new low QC level was set to 90.0 ng/mL.	
Hemolysis effect	Not reported	
Lipemic effect	Not reported	
Interference & specificity	Not reported	

Dilution linearity & hook effect	Highest concentration tested at 15.2 µg/mL with dilution factors from 8 to 400. Range of observed bias was -10.3 to -15.1% of nominal concentration. No hook effect was observed up to 15.2 µg/mL
Bench-top/process stability	Stable up to 24 hours at room temperatures. Stability was assessed using stability QCs prepared at 30 and 1800 ng/mL and the observed %bias ranged from -14.3 to 3.35% of nominal concentrations.
Freeze-Thaw stability	Stable up to 5 cycles. Stability was assessed using stability QCs prepared at 30 and 1800 ng/mL and the observed %bias ranged from 0.616 to 1.37% of nominal concentrations
Long-term storage	Stability was assessed using stability QCs with 30 and 1800 ng/mL up to 213 (525) days at 80±10°C. Longer duration for analyte storage stability was extensively assessed in studies RCQG5, 3, and 7
Parallelism	Not applicable.
Method performance in clinical study E7777-J081-101 (Sample testing report IDs:W-20160010/ UDZ)	
Assay passing rate	89% (16 out of 18 runs including ISR)
Standard curve performance	Cumulative bias range: -2.00 to 2.16% and -4.80 to 4.25% Cumulative precision: ≤ 8.08 and 6.28% CV
QC performance	Cumulative bias range: -12.00 to -9.81% and 2.98 to 6.93% Cumulative precision: ≤ 7.56 and 6.93% CV TE: ≤ 19.56 and 14.95%
Method reproducibility	Incurred sample reanalysis was performed in ~12% of study samples and 91 % of samples met the pre-specified criteria
Study sample analysis/stability	275 original and 275 back-up samples were received frozen at bioanalytical site in good condition from (b) (4) and (b) (4) between 20 April 2012 and 19 August 2015 and stored frozen at (b) (4) within established storage duration except at the time for analyses.

19.4.2. Pharmacometrics Review

19.4.2.1. Results of Sponsor's Analysis

19.4.2.1.1. Population PK analysis

The Population PK Analysis Dataset included 1427 serum E7777 observations from 155 patients from Study E7777-J081-101 (hereafter referred to as Study 101), Study 205, and Study E7777-G000-302 [hereafter referred to as Study 302]. Table 36 summarizes the number of subjects and corresponding PK observations by study (including Lead-In part or Main Study for Study 302) and treatment group. Subject dosing and demographic disposition are presented in Table 37. Laboratory and disease characteristics are summarized in Table 38 with median and range for continuous variables and number of subjects (n) and frequency (%) for categorical variables. Most of the data were obtained at the 9 mcg/kg/day group and demographics were generally balanced.

Table 36: Number of Subjects and PK Samples per Subject by Study and Treatment Group for the Population PK Analysis Dataset

Study	Treatment Group (µg/kg/day)	Lead-in Phase	n (subjects)	Median PK observation per subject	Min PK samples per subject	Max PK samples per subject	Total PK samples
101	6	NA	3	22.0	14	29	65
101	9	NA	7	15.0	13	35	148
101	12	NA	3	14.0	13	22	49
205	9	NA	37	7.0	2	21	301
302	6	1	2	29.5	27	32	59
302	9	0	84	2.0	1	31	412
302	9	1	8	30.5	17	32	222
302	12	1	9	9.0	8	32	156
302	15	1	2	7.5	7	8	15

Max = maximum, Min = minimum, NA = not applicable. Table reflects data prior to pharmacokinetic (PK) analysis exclusion. See Section 13.1.1 for the data listing presenting PK data from 2 subjects excluded from the PK analysis.

Source: cpms-e7777-001r-v1, Table 5

Table 37: Summary of Demographic Variables for the Population PK Analysis Dataset

	101, N = 13	205, N = 37	302, N = 105	Overall, N = 155
E7777 Dose Group				
6 µg/kg/day	3 (23%)	0 (0%)	2 (1.9%)	5 (3.2%)
9 µg/kg/day	7 (54%)	37 (100%)	92 (88%)	136 (88%)
12 µg/kg/day	3 (23%)	0 (0%)	9 (8.6%)	12 (7.7%)
15 µg/kg/day	0 (0%)	0 (0%)	2 (1.9%)	2 (1.3%)
Age (years)	64 (23, 75)	65 (27, 82)	64 (26, 86)	64 (23, 86)
Body Weight (kg)	57 (45, 73)	60 (39, 84)	83 (49, 148)	74 (39, 148)
Body Surface Area (m ²)	1.57 (1.41, 1.87)	1.67 (1.28, 1.97)	1.94 (1.42, 2.71)	1.81 (1.28, 2.71)
Missing	0	0	39	39
Body Mass Index (kg/m ²)	22.0 (16.0, 29.1)	22.8 (16.8, 30.9)	29.6 (21.4, 73.1)	25.4 (16.0, 73.1)
Missing	0	0	39	39
Female	5 (38%)	12 (32%)	43 (41%)	60 (39%)
Race				
White	0 (0%)	0 (0%)	79 (75%)	79 (51%)
African American/Black	0 (0%)	0 (0%)	19 (18%)	19 (12%)
Japanese	13 (100%)	37 (100%)	0 (0%)	50 (32%)
Other	0 (0%)	0 (0%)	7 (6.7%)	7 (4.5%)
Asian - Non-Japanese	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)

n (%) applicable to categorical covariates dose, sex and race; Continuous variables are summarized as median (minimum, maximum). Table reflects data prior to pharmacokinetic (PK) analysis exclusion. See Section 13.1.1 for the data listing presenting PK data from 2 subjects excluded from the PK analysis.

Source: cpms-e7777-001r-v1, Table 6

Table 38: Summary of Liver Function and Disease Variables for the Population PK Analysis Dataset

	101, N = 13	205, N = 37	302, N = 105	Overall, N = 155
Creatinine clearance (mL/min)	85 (38, 125)	89 (34, 168)	103 (24, 369)	96 (24, 369)
Serum creatinine (µMol/L)	62 (41, 142)	65 (33, 129)	71 (44, 168)	71 (33, 168)
Bilirubin (µMol/L)	10.4 (5.1, 22.1)	8.6 (3.4, 25.6)	5.0 (1.7, 21.2)	6.2 (1.7, 25.6)
Albumin (g/L)	38.0 (31.0, 47.0)	40.0 (31.0, 46.0)	40.0 (24.0, 49.0)	40.0 (24.0, 49.0)
Aspartate aminotransferase (U/L)	25 (16, 71)	23 (14, 73)	22 (9, 83)	23 (9, 83)
Alkaline phosphatase (U/L)	262 (162, 400)	237 (118, 421)	73 (29, 427)	87 (29, 427)
Disease history				
CTCL	3 (23%)	19 (51%)	105 (100%)	127 (82%)
PTCL	10 (77%)	17 (46%)	0 (0%)	27 (17%)
Other	0 (0%)	1 (2.7%)	0 (0%)	1 (0.6%)
ECOG performance score				
0	11 (85%)	24 (65%)	59 (56%)	94 (61%)
1	2 (15%)	13 (35%)	45 (43%)	60 (39%)
2	0 (0%)	0 (0%)	1 (1.0%)	1 (0.6%)
Prior anticancer therapy				
Unknown	0 (0%)	37 (100%)	0 (0%)	37 (24%)
No	1 (7.7%)	0 (0%)	3 (2.9%)	4 (2.6%)
Yes	12 (92%)	0 (0%)	102 (97%)	114 (74%)
Prior radiation therapy	3 (23%)	13 (35%)	44 (42%)	60 (39%)

Categorical variables are summarized as n (%); Continuous variables are summarized as median (minimum, maximum). Table reflects data prior to pharmacokinetic (PK) analysis exclusion. See Section 13.1.1 for the data listing presenting PK data from 2 subjects excluded from the PK analysis.

CTCL = cutaneous T-cell lymphoma, ECOG = Eastern Cooperative Oncology Group, PTCL = peripheral T-cell lymphoma.

Source: cpms-e7777-001r-v1, Table 7

To reflect the attenuating profiles of E7777 upon multiple administration in the presence of anti-E7777 antibodies, the PK model incorporated an empirical, time-varying clearance component. Several commonly employed time varying clearance relationships were assessed during the model building steps. The clearance function per equation 1 adequately described the time varying E7777 clearance profiles, characterized by a change from an initial (CL_{ini}) to a new 'steady state' value as a function of time (CL_{ss}) as an exponential function of time. Time is the day of treatment, starting on day 0, corresponding to Cycle 1, Day 1. Mean residence time (MRT) is a parameter representing the 1/rate of approach to CL_{ss} from CL_{ini}.

$$CL = CL_{ss} - (CL_{ss} - CL_{ini}) * \exp\left(-\frac{Time}{MRT}\right) \quad \text{equation(1)}$$

The base PK model incorporated a 2-compartment distribution model with infusion rate input into the central compartment derived from infusion duration and daily administered amounts of E7777, most commonly over 1 hour. The PK model was informed by data over a range of doses (6 to 15mcg/kg/day) in subjects with CTCL and PTCL. The tested covariates included

effect of body weight on volume parameters and age, sex, race, body weight, Eastern Cooperative Oncology Group (ECOG) Performance Status, albumin, creatinine clearance, and total serum bilirubin concentration on both the initial (CLini) and steady state (CLss) clearance parameters. The covariates remained in the final model were body weight on CLini, V1, V2, and CLss as well as albumin on CLini and CLss. The summary of parameter estimates of the final population PK model are listed in Table 39. The goodness-of-fit plots are shown in Figure 10, Figure 11, and Figure 12. Figure 13 shows the visual predictive check (VPC). The PK profile over 6 cycles for a typical patient with 75kg body weight receiving 9 mcg/kg/day treatment can be seen in Figure 14.

Table 39: Final Population PK Model Parameters

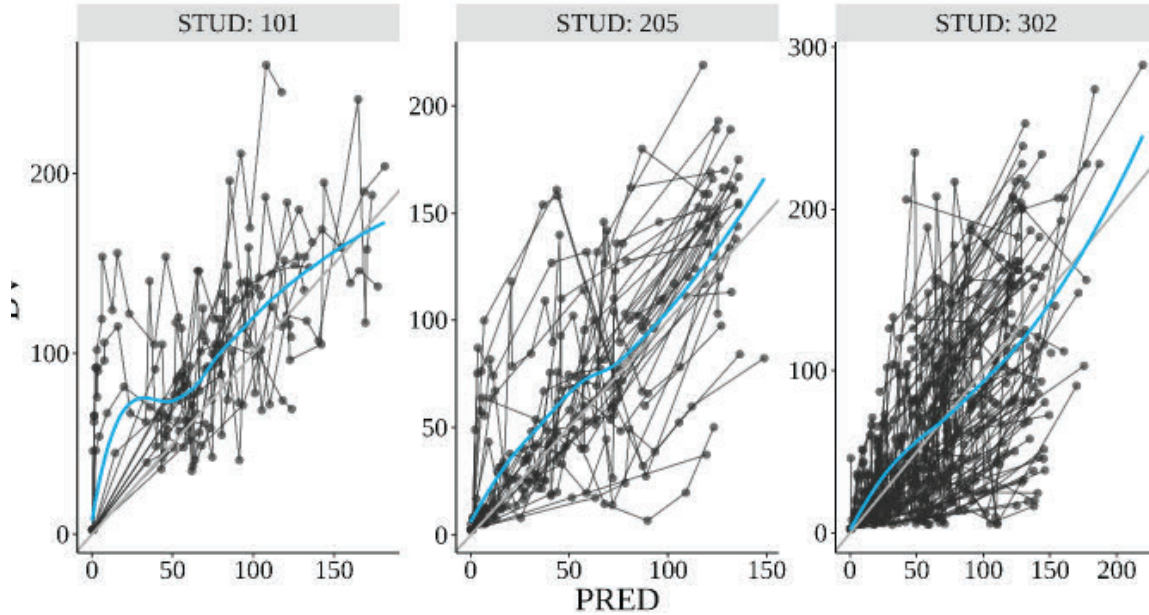
Parameter	NONMEM		Bootstrap		
	Estimate	RSE (%)	Median	5 th	95 th
Inter-compartmental clearance (Q; L/h)	8.17	5.91	8.50	3.90	16.6
Lag time for central compartment (ALAG1; h)	0.41	2.07	0.42	0.206	0.820
Initial central clearance (CLini; L/h)	1.31	14.2	1.29	-0.76	3.34
'Steady-State' clearance (CLss; L/h)	9.85	20.6	9.06	-4.4	25.8
MRT to CLss (T50_CL; day)	77.5	49.0	84.45	-156	368
Proportional residual error for Studies 101 and 205	0.218	3.34	0.224	0.138	0.299
Proportional residual error for Study 302	0.390	3.52	0.384	0.260	0.511
Covariate Effects					
Body weight on CLini	1.52	34.0	1.67	0.01	3.06
Body weight on V1	1.53	89.9	1.67	-0.71	3.52
Body weight on V2	0.867	27.5	0.81	0.38	1.30
Body weight on CLss	0.067	472	0.03	-1.57	1.81
Albumin on CLini	1.74	11.7	1.28	-0.21	3.60
Albumin on CLss	1.74	31.6	1.78	-0.38	3.90
Random Effects (Omega)					
Central volume of distribution (V1)	1.46	38.4	3.95	-2.44	7.31
Peripheral volume of distribution (V2)	0.317	14.2	0.098	-0.95	1.16
covariance (V2~Q)	0.552	42.1	0.059	-0.58	0.74
Inter-compartmental clearance (Q)	0.407	15.9	0.17	-6.26	6.59
Initial central clearance (CLini)	0.974	9.14	0.95	-64.1	66.0
Steady-State' clearance (CLss)	0.635	31.9	0.52	-61.3	62.2
MRT to CLss (T50)	2.43	17.7	7.05	-1140	1150
MRT = mean residence time, NONMEM = non-linear mixed-effects modeling, PK = pharmacokinetic, RSE = residual standard error					

Source: cpms-e7777-001r-v1, Table 11

Figure 10: DV vs. PRED (top)/iPRED (bottom) for the Final Population Model Stratified by Study

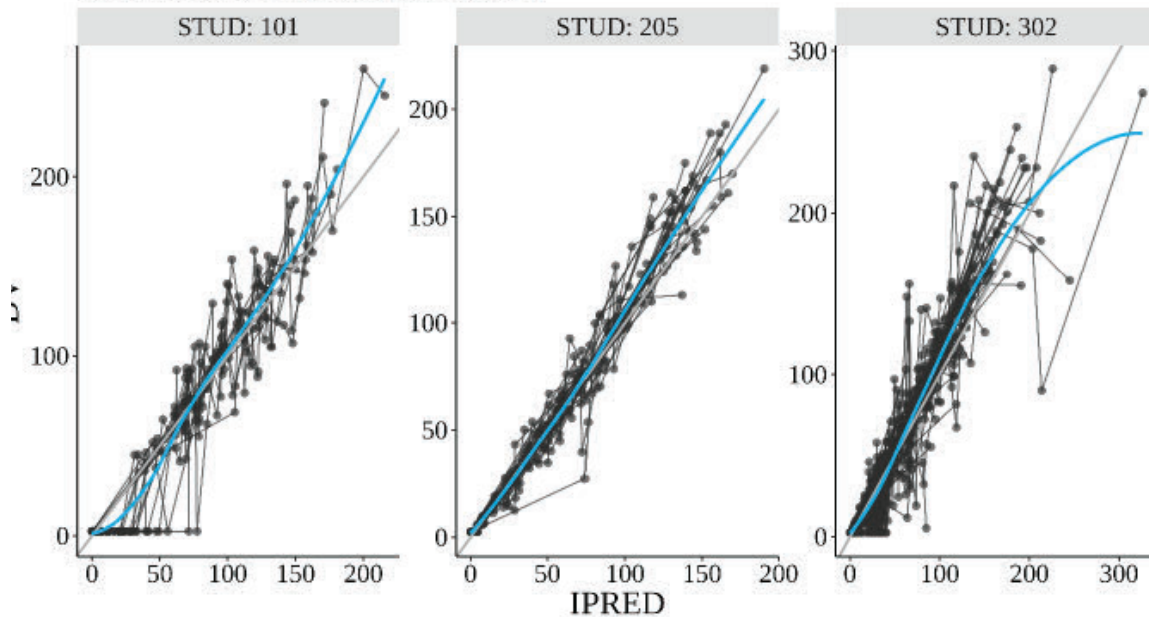
DV vs. PRED | 0275

Ofv: 7173.140



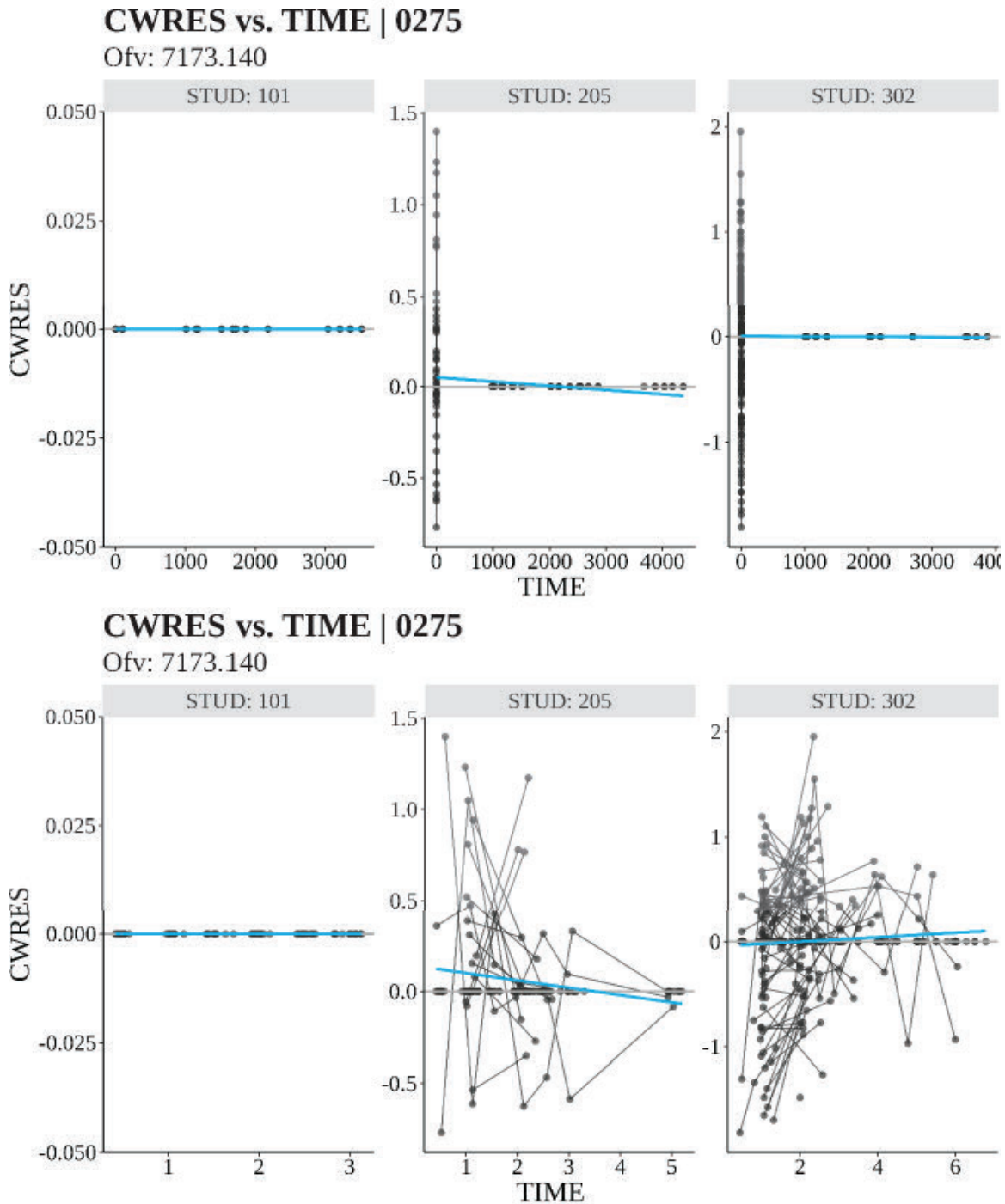
DV vs. IPRED | 0275

Ofv: 7173.140, Eps shrink: 14.3 [1]



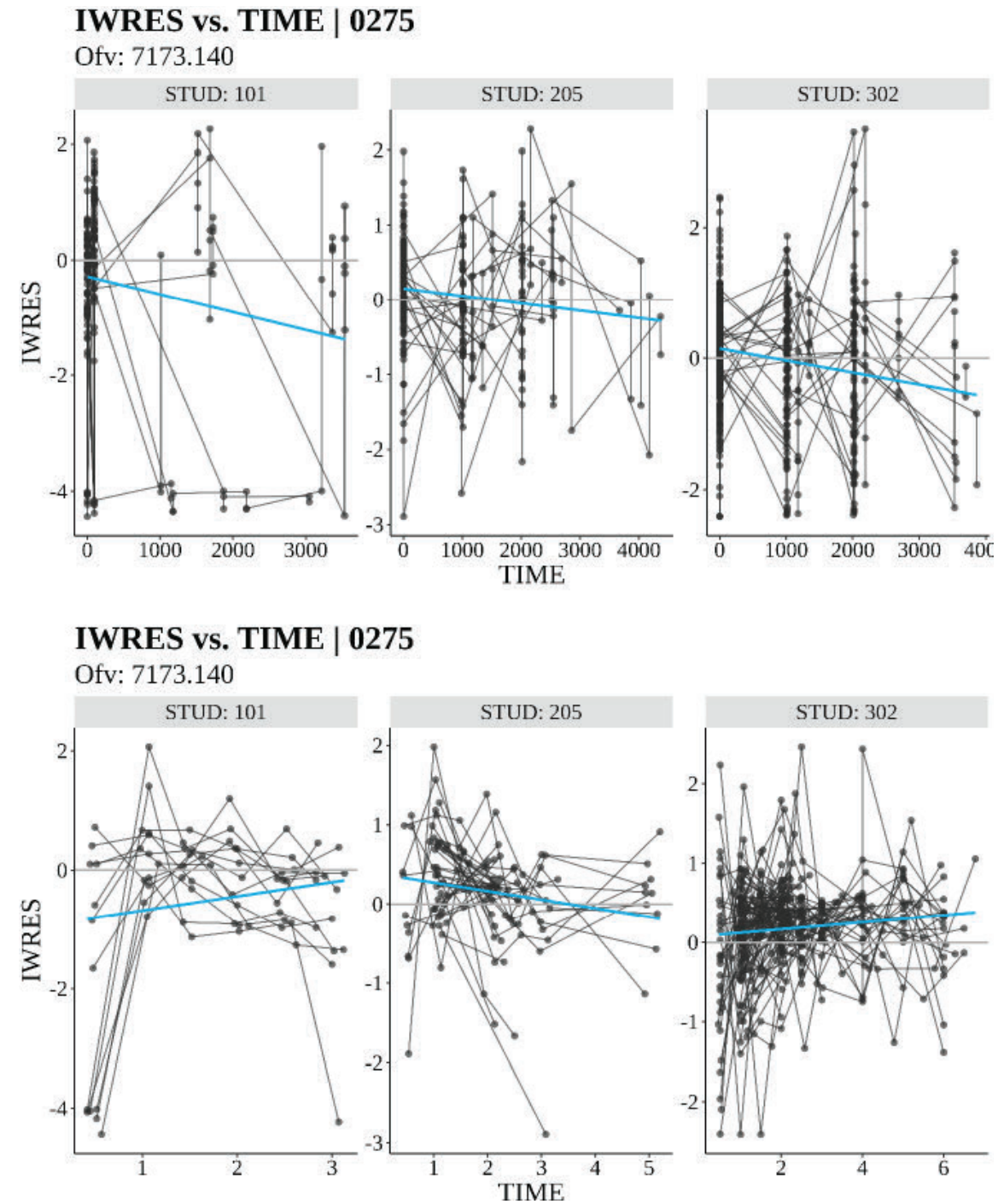
Source: cpms-e7777-001r-v1, Suppl Figure 11

Figure 11: CWRES vs. Time for the Final Population Model Stratified by Study



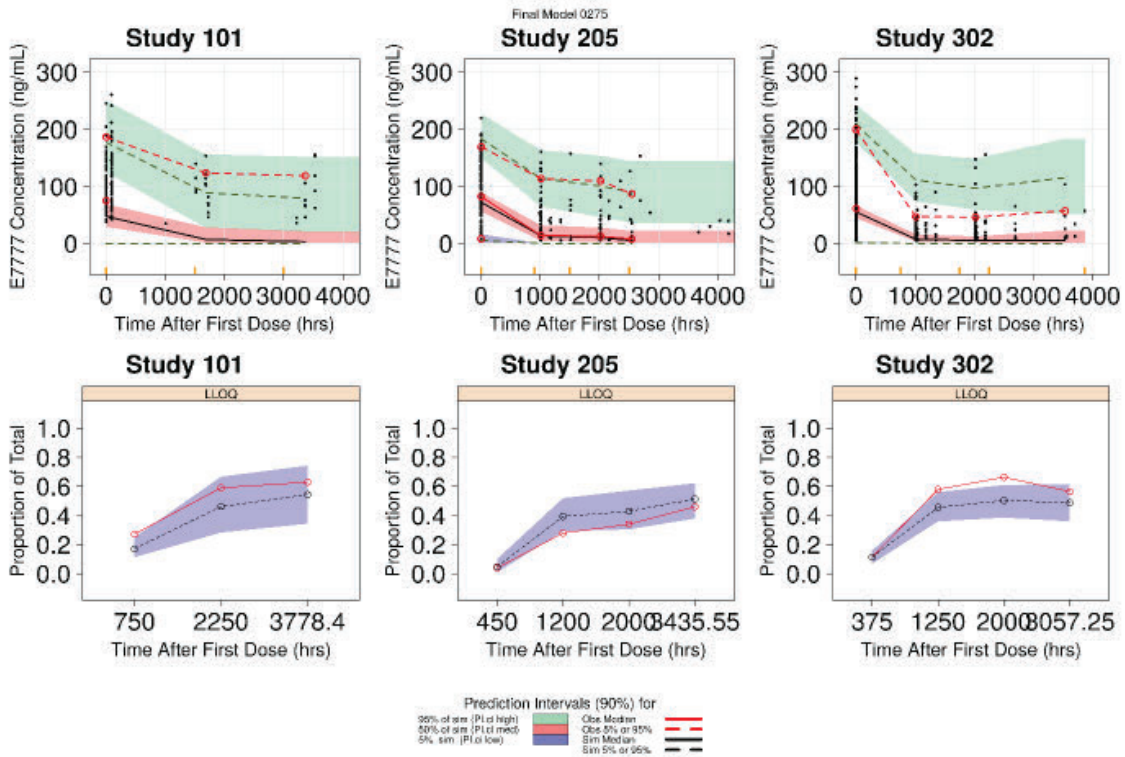
Source: cpms-e7777-001r-v1, Suppl Figure 12

Figure 12: IWRES vs. Time for the Final Population Model Stratified by Study



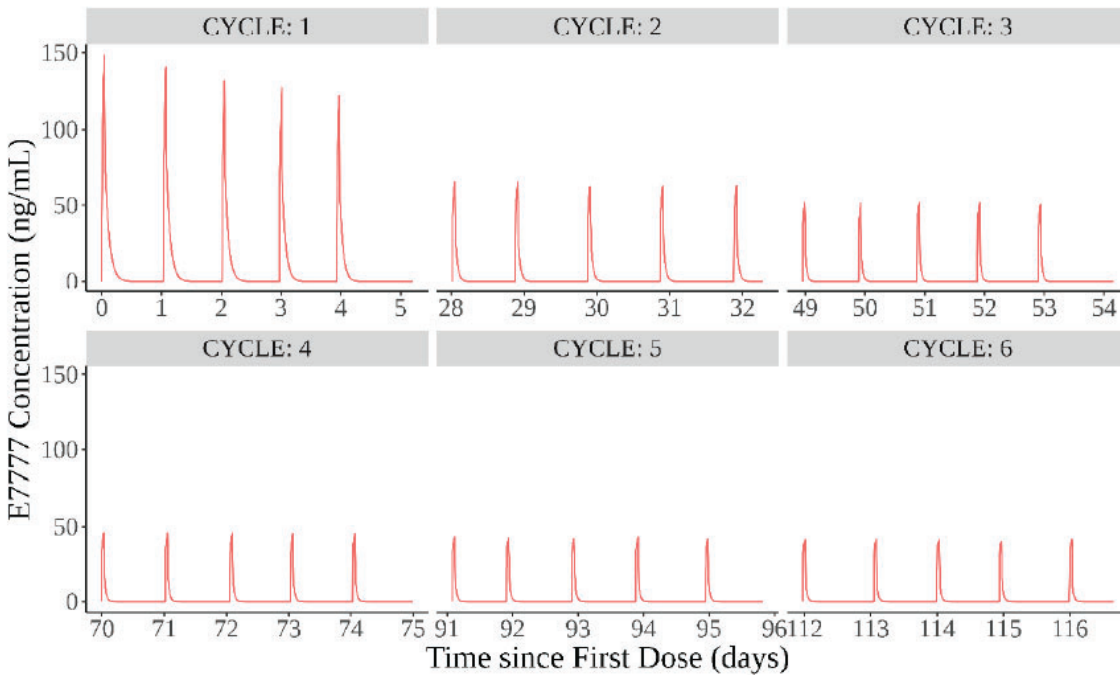
Source: cpms-e7777-001r-v1, Suppl Figure 13

Figure 13: Visual Predictive Check for the Final Population PK Model Stratified by Study



Source: cpms-e7777-001r-v1, Suppl Figure 15

Figure 14: Typical Patient E7777 Plasma Concentration Over Time Profile Over 6 Cycles of Treatment with 9 mcg/kg/day E7777

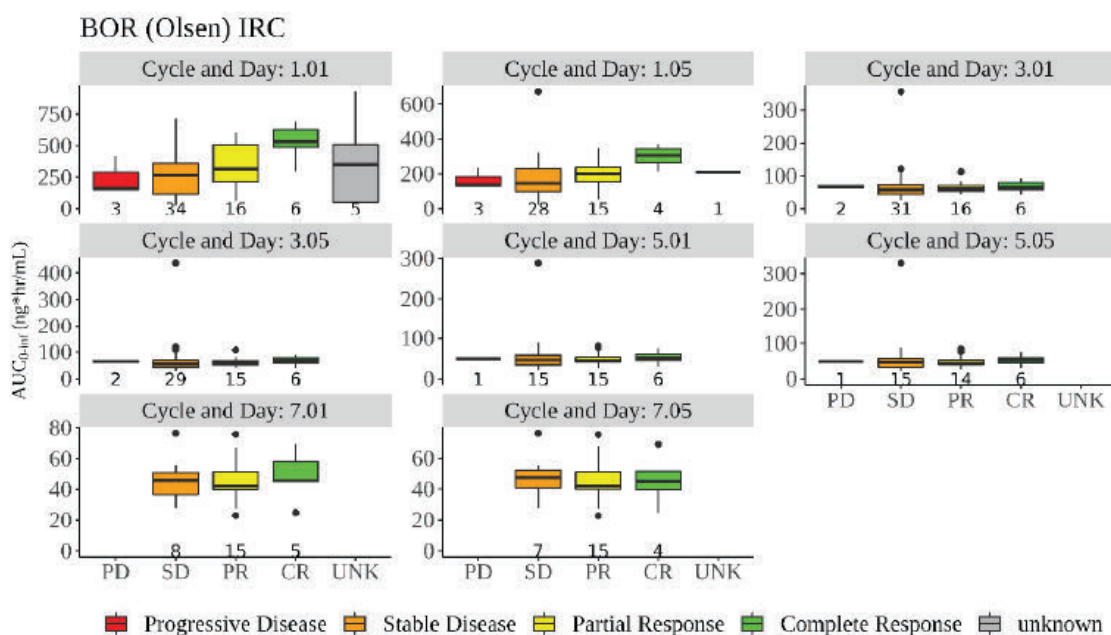


Source: cpms-e7777-001r-v1, Figure 2

19.4.2.1.2. Exposure-response analysis for efficacy

The relationships of E7777 exposure and key efficacy and safety endpoints were graphically examined. At the 9 mcg/kg/day dose, complete responders exhibited consistently higher E7777 exposures (C_{max} and AUC_{0-inf}) over partial and stable responders and individuals classified with progressive disease at day 1 and day 5 during cycle 1 (Figure 15).

Figure 15: Predicted E7777 AUC_{0-inf} vs. Best Observed Response (BOR) per Olsen Criteria Assessed by IRC



Source: cpms-e7777-001r-v1, Figure 5

19.4.2.1.3. Exposure-response analysis for safety

The dataset for the ER analysis for safety contains data from all subjects with CTCL, PTCL, or other lymphomas across E7777 studies, who received E7777 at any dose level (6, 9, 12, 15 mcg/kg). The deposit of the patients are 111 patients from study E7777-G000-302 (9 mcg/kg: n=98, 6 mcg/kg: n=2, 12 mcg/kg: n=9, 15 mcg/kg: n=2), 13 patients from study E7777-J081-101 (9 mcg/kg: n=7, 6 mcg/kg: n=3, 12 mcg/kg: n=3), and 37 patients from study E7777-J081-205 (9 mcg/kg: n=37). The demographic information is summarized in Table 40 and Table 41. The summary of the adverse events of special interest (AESI) is shown in Table 42.

Table 40: Summary of Demographic Variables of the ER for Safety Dataset

Demographic Vars.	Study 101 N = 13 ^a	Study 205 N = 37 ^a	Study 302 N = 111 ^a	Overall N = 161 ^a
E7777 Dose Group				
12 ug/kg/day	3 (23%)	0 (0%)	9 (8.1%)	12 (7.5%)
15 ug/kg/day	0 (0%)	0 (0%)	2 (1.8%)	2 (1.2%)
6 ug/kg/day	3 (23%)	0 (0%)	2 (1.8%)	5 (3.1%)
9 ug/kg/day	7 (54%)	37 (100%)	98 (88%)	142 (88%)
E7777 Starting Dose (mg)^b	541 (279, 653)	537 (349, 752)	750 (389, 1,368)	660 (279, 1,368)
E7777 Study 302 Lead-In	0 (0%)	0 (0%)	21 (19%)	21 (13%)
Age (years)	64 (23, 75)	65 (27, 82)	65 (26, 87)	65 (23, 87)
Body Weight (kg)	57 (45, 73)	60 (39, 84)	83 (49, 148)	74 (39, 148)
Body Surface Area (m²)	1.57 (1.41, 1.87)	1.67 (1.28, 1.97)	1.94 (1.42, 2.71)	1.82 (1.28, 2.71)
missing	0	0	41	41
Body Mass Index (kg/m²)	22.0 (16.0, 29.1)	22.8 (16.8, 30.9)	29.5 (21.4, 73.1)	25.5 (16.0, 73.1)
missing	0	0	41	41
Female	5 (38%)	12 (32%)	45 (41%)	62 (39%)
Race				
White	0 (0%)	0 (0%)	82 (74%)	82 (51%)
AA/Black	0 (0%)	0 (0%)	20 (18%)	20 (12%)
Japanese	13 (100%)	37 (100%)	0 (0%)	50 (31%)
Other	0 (0%)	0 (0%)	7 (6.3%)	7 (4.3%)
Asian - Non Japanese	0 (0%)	0 (0%)	1 (0.9%)	1 (0.6%)
Missing	0 (0%)	0 (0%)	1 (0.9%)	1 (0.6%)

AA = African American, CTCL = cutaneous T-cell lymphoma, PTCL = peripheral T-cell lymphoma, Vars = variables

a: n (%) or Median (Range)

b: Starting dose in mg ($\mu\text{g}/\text{kg}$ *individual body weight)

Source: 1114-multiple-module-info-amendment, Table 1

Table 41: Summary of Disease and Laboratory Variables of the ER for Safety Dataset

Disease Variables	Study 101 N = 13 ^a	Study 205 N = 37 ^a	Study 302 N = 111 ^a	Overall N = 161 ^a
E7777 Dose Group				
12 ug/kg/day	3 (23%)	0 (0%)	9 (8.1%)	12 (7.5%)
15 ug/kg/day	0 (0%)	0 (0%)	2 (1.8%)	2 (1.2%)
6 ug/kg/day	3 (23%)	0 (0%)	2 (1.8%)	5 (3.1%)
9 ug/kg/day	7 (54%)	37 (100%)	98 (88%)	142 (88%)
Disease History				
CTCL	3 (23%)	19 (53%)	111 (100%)	133 (83%)
PCTL	10 (77%)	17 (47%)	0 (0%)	27 (17%)
other ^b	0	1 ^b	0	1 ^b
CTCL Type				
MF	3 (100%)	14 (74%) ^c	84 (76%)	101 (76%)
SS	0 (0%)	1(5.3%) ^c	27 (24%)	28 (21%)
Other CTCL	0 (0%)	4 (21%) ^c	0 (0%)	4 (3.0%)
PCTL and other ^b	10	17+1 ^b	0	28
ECOG Status				
0	11 (85%)	24 (65%)	61 (55%)	96 (60%)
1	2 (15%)	13 (35%)	49 (44%)	64 (40%)
2	0 (0%)	0 (0%)	1 (0.9%)	1 (0.6%)
Cancer Staging				
IA	0 (0%)	2 (5.4%)	5 (4.5%)	7 (4.3%)
IB	0 (0%)	0 (0%)	18 (16%)	18 (11%)
II	0 (0%)	1 (2.7%)	0 (0%)	1 (0.6%)
IIA	0 (0%)	0 (0%)	11 (9.9%)	11 (6.8%)
IIB	0 (0%)	11 (30%)	28 (25%)	39 (24%)
III	0 (0%)	8 (22%)	0 (0%)	8 (5.0%)
IIIA	0 (0%)	2 (5.4%)	9 (8.1%)	11 (6.8%)
IIIB	0 (0%)	0 (0%)	8 (7.2%)	8 (5.0%)
IV	0 (0%)	8 (22%)	0 (0%)	8 (5.0%)
IVA	0 (0%)	2 (5.4%)	6 (5.4%)	8 (5.0%)
IVA1	0 (0%)	0 (0%)	17 (15%)	17 (11%)

Disease Variables	Study 101 N = 13 ^a	Study 205 N = 37 ^a	Study 302 N = 111 ^a	Overall N = 161 ^a
IVA2	0 (0%)	0 (0%)	7 (6.3%)	7 (4.3%)
IVB	0 (0%)	2 (5.4%)	2 (1.8%)	4 (2.5%)
missing	13 (100%)	1 (2.7%)	0 (0%)	14 (8.7%)
Prior Anticancer Therapies (n)	NA (Inf, -Inf)	NA (Inf, -Inf)	5 (1, 18)	5 (1, 18)
missing	13	37	0	50
Baseline Albumin	38.0 (31.0, 47.0)	40.0 (31.0, 46.0)	40.0 (24.0, 49.0)	40.0 (24.0, 49.0)
Alkaline Phosphatase (U/L)	262 (162, 400)	237 (118, 421)	73 (29, 427)	88 (29, 427)
Aspartate Aminotransferase (U/L)	25 (16, 71)	23 (14, 73)	22 (9, 83)	23 (9, 83)
Alanine Transaminase	25 (10, 119)	18 (6, 76)	21 (7, 82)	20 (6, 119)
Bilirubin	10.4 (5.1, 22.1)	8.6 (3.4, 25.6)	5.1 (1.7, 21.2)	6.2 (1.7, 25.6)
Serum Creatinine	62 (41, 142)	65 (33, 129)	71 (35, 168)	71 (33, 168)
Creatinine Clearance	85 (38, 125)	89 (34, 168)	102 (24, 369)	95 (24, 369)

CTCL = cutaneous T-cell lymphoma, ECOG = Eastern Cooperative Oncology Group, MF = mycosis fungoides, PTCL = peripheral T-cell lymphoma, SS = Sezary syndrome

a: n (%); Median (Range)

b: Disease History, 'other' (n=1) Study 205 represents 'Extranodal NK/T cell lymphoma of nasal type (ENKL)'

c: Study 205 'CTCL type by Investigator'; Study 205 Clinical Study Report Table 7 presents 'CTCL type by Central Reader'

Source: 1114-multiple-module-info-amendment, Table 2

Table 42: Summary of Adverse Events of Special Interest of the ER for Safety Dataset

Variable	Study 101 N = 13 ^a	Study 205 N = 37 ^a	Study 302 N = 111 ^a	Overall N = 161 ^a
E7777 Dose Group				
12 ug/kg/day	3 (23%)	0 (0%)	9 (8.1%)	12 (7.5%)
15 ug/kg/day	0 (0%)	0 (0%)	2 (1.8%)	2 (1.2%)
6 ug/kg/day	3 (23%)	0 (0%)	2 (1.8%)	5 (3.1%)
9 ug/kg/day	7 (54%)	37 (100%)	98 (88%)	142 (88%)
Capillary Leak Syndrome	7 (54%)	15 (41%)	28 (25%)	50 (31%)
Hepatotoxicity	12 (92%)	33 (89%)	39 (35%)	84 (52%)
Visual Impairment	3 (23%)	1 (2.7%)	9 (8.1%)	13 (8.1%)
Infusion Reaction	9 (69%)	20 (54%)	76 (68%)	105 (65%)
Hypersensitivity	8 (62%)	21 (57%)	70 (63%)	99 (61%)
Infection	0 (0%)	6 (16%)	14 (13%)	20 (12%)
Thrombotic Events	0 (0%)	0 (0%)	4 (3.6%)	4 (2.5%)
Rash	4 (31%)	2 (5.4%)	19 (17%)	25 (16%)
Serious TEAE	2 (15%)	13 (35%)	31 (28%)	46 (29%)
Time to AE (days) ^b	3 (1, 5)	5 (1, 44)	3 (1, 127)	4 (1, 127)
missing	0	0	10	10
ADA Titer Anti-E7777	4 (0, 32)	13 (1, 274,432)	222 (1, 1,305,600)	80 (0, 1,305,600)
missing	0	6	15	21
ADA Titer Anti-IL-2	154 (13, 1,900)	27 (1, 729)	27 (1, 6,561)	27 (1, 6,561)
missing	5	17	35	57
Best Response in Last Therapy				
COMPLETE RESPONSE	5 (38%)	0 (0%)	2 (1.8%)	7 (4.3%)
UNKNOWN	1 (7.7%)	1 (2.7%)	32 (29%)	34 (21%)
PARTIAL RESPONSE	2 (15%)	4 (11%)	26 (23%)	32 (20%)
STABLE DISEASE	3 (23%)	5 (14%)	23 (21%)	31 (19%)
PROGRESSIVE DISEASE	2 (15%)	4 (11%)	23 (21%)	29 (18%)
missing	0 (0%)	23 (62%)	0 (0%)	23 (14%)

Source: 1114-multiple-module-info-amendment, Table 3

Variable	Study 101 N = 13 ^a	Study 205 N = 37 ^a	Study 302 N = 111 ^a	Overall N = 161 ^a
NOT EVALUABLE	0 (0%)	0 (0%)	2 (1.8%)	2 (1.2%)
NOT APPLICABLE	0 (0%)	0 (0%)	3 (2.7%)	3 (1.9%)
Progression in Last Therapy^c				
missing	13 (100%)	37 (100%)	0 (0%)	50 (31%)
Yes	0 (0%)	0 (0%)	46 (41%)	46 (29%)
No	0 (0%)	0 (0%)	28 (25%)	28 (17%)
Unknown	0 (0%)	0 (0%)	37 (33%)	37 (23%)
Duration of Last Therapy (days)	NA (Inf, -Inf)	10 (2, 74)	5 (0, 248)	6 (0, 248)
missing	13	23	0	36

ADA = antidrug antibody, AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, CTCL = cutaneous T-cell lymphoma, PTCL = peripheral T-cell lymphoma

a: n (%) or Median (Range)

b: Time to AE (days) based on time to first TEAE, Best Response in last Therapy is last prior anticancer therapy before study entry,

c: Progression in or Duration of Last Therapy (last anticancer therapy, prior to E7777 study start)

Multivariate logistic regression analyses were performed to explore the correlation between the E7777 PK exposures (C_{max} and daily average concentration C_{avg}) and the safety outcomes, including leak syndrome (CLS), hepatotoxicity, visual impairment, infusion reactions, hypersensitivity, infections, rash events. The models included a set of prespecified predictor variables: age, body weight at baseline, sex, race, disease history, ECOG performance status, baseline albumin, baseline alkaline phosphatase, baseline aspartate aminotransferase, baseline alanine transaminase, baseline bilirubin and baseline serum creatinine. The final model was selected based on Akaike Information Criterion (AIC). Log odds of CLS were associated with a 7% increase for a unit of E7777 exposure (C_{avg}). The logtransformed E7777 concentrations on Cycle 1 Day 1 were associated with an increased probability of hepatotoxicity, odds ratio (OR) estimate 2.9. Conversely, the incidence of infusion reactions was negatively associated with E7777 concentrations under the proposed models (OR=0.37). For other endpoints, the E7777 exposure OR was close to 1 with the 95% confidence interval including 1.

Reviewer's comment:

- *The reviewer reproduced the Applicant's proposed population PK model with the PK parameter estimates reasonably close to Applicant's. No major bias was identified. However, the eta shrinkage for V1, V2, Q, CLs, and T50 were larger than 35%. As a result, the estimated individual PK metrics should be used with caution. Body weight was estimated as a covariate for clearance and volume distribution parameters. In addition, the initial and steady state CL were affected by albumin. The impact of these covariates are not considered clinically relevant.*

- The reviewer performed independent population PK analyses to evaluate the labeling statements and to support the review questions evaluation. Refer to the Reviewer’s Analysis for details.
- Applicant’s graphic examination of the correlation between E7777 PK exposure and efficacy endpoint suggested that a positive exposure-response relationship may exist for E7777. The reviewer did independent analyses to explore the potential exposure-response correlation for efficacy. Refer to the Reviewer’s Analysis for details.
- The reviewer performed exposure-response analyses for safety with more PK metrics tested. Refer to the Reviewer’s Analysis for details.

19.4.2.2. Reviewer’s Analysis

19.4.2.2.1. Background

The primary clinical study in this submission is a single-arm, Phase 3 clinical study of E7777 in subjects with persistent or recurrent CTCL (Study 302). Study 302 included a Lead-In part and a Main Study. The results of 2 supportive studies conducted in Japan in patients with peripheral T-cell lymphoma (PTCL) or CTCL, and which were the basis of marketing approval in Japan, are included in this submission: a Phase 1 dose selection study (Study 101) and a Phase 2 efficacy and safety study (Study 205). The summary of the key efficacy and safety results are summarized in Table 43 and 44. It was noted that the 6 mcg/kg/day showed comparable efficacy and safety profile compared with 9 mcg/kg/day based on data from a limited number of patients. In this review, the appropriateness of alternative dosing regimens, including 6 mcg/kg/day, for the proposed indication was evaluated.

Table 43: Summary of the Efficacy Results for E7777 Clinical Programs

Trial	Patient population and region	Dose (mcg/kg/day)	N	CR, n(%)	PR, n(%)	SD, n(%)	PD, n(%)	ORR, n(%)
H081-101	T-cell lymphoma in Japanese	6	3	0	2 (66.7)	0	1 (33.3)	2 (66.7)
		9	7	0	2 (28.6)	2 (28.6)	2 (28.6)	2 (28.6)
		12	3	0	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)
J081-205	Relapsed or refractory PTCL and CTCL	9	19*	0	6 (31.6)	10 (52.6)	1 (5.3)	6 (31.6)
G000-302 lead-in	Recurrent or persistent CD25 positive CTCL in US and Australia	6	2	1 (50)	0	1 (50)	0	1 (50)
		9	8	0	4 (50)	4 (50)	0	4 (50)
		12	7	0	3 (42.9)	1 (14.3)	1 (14.3)	3 (42.9)
		15	1	0	0	0	1 (100)	0
G000-302		9	69	6 (8.7)	19 (27.5)	36 (52.2)	3 (4.3)	25 (36.2)

*: CTCL only

Source: Reviewer’s analysis

Table 44: Summary of the Safety Results for E7777 Clinical Programs

Trial	Patient population and region	Dose (mcg/kg/day)	N	TEAE, n(%)	TE-SAE [#] , n(%)	Withdrawal, n(%)	Reduction, n(%)	Interruption, n(%)
H081-101	T-cell lymphoma in Japanese	6	3	3 (100)	1 (33.3)	1 (33.3)	0	0
		9	7	7 (100)	3 (42.9)	1 (14.3)	1 (14.3)	2 (28.6)
		12	3	3 (100)	1 (33.3)	1 (33.3)	2 (66.7)	0
J081-205	Relapsed or refractory PTCL and CTCL	9	19*	19 (100)	8 (42.1)	10 (52.6)	1 (5.3)	6 (31.6)
G000-302 lead-in	Recurrent or persistent CD25 positive CTCL in US and Australia	6	2	2 (100)	0	0	0	0
		9	8	8 (100)	3 (37.5)	0	0	0
		12	9	9 (100)	4 (44.4)	2 (22.2)	0	3 (33.3)
		15	2	2 (100)	2 (100)	2 (100)	1 (50)	2 (100)
G000-302		9	69	68 (98.6)	26 (37.7)	8 (11.6)	3 (4.3)	26 (37.7)

*: CTCL only

#: treatment-emergent serious AE, including life-threatening, inpatient hospitalization, disability or incapacity, important medical events, etc.

Source: Reviewer's analysis

In Study 302, the Applicant reported 92.9% (78/84) and 82.1% (69/84) of patients developed new or increased antibodies against E7777 and IL-2 following the E7777 treatment (9 mcg/kg QD) initiation. In reviewer's analysis, 30 out of 37 and 107 out of 112 of all available patients from Study 205 and Study 302 were identified at least one observation with positive anti-E7777 antibody. Due to the high prevalence, the effect of ADA on PK, efficacy, and safety was evaluated in this review.

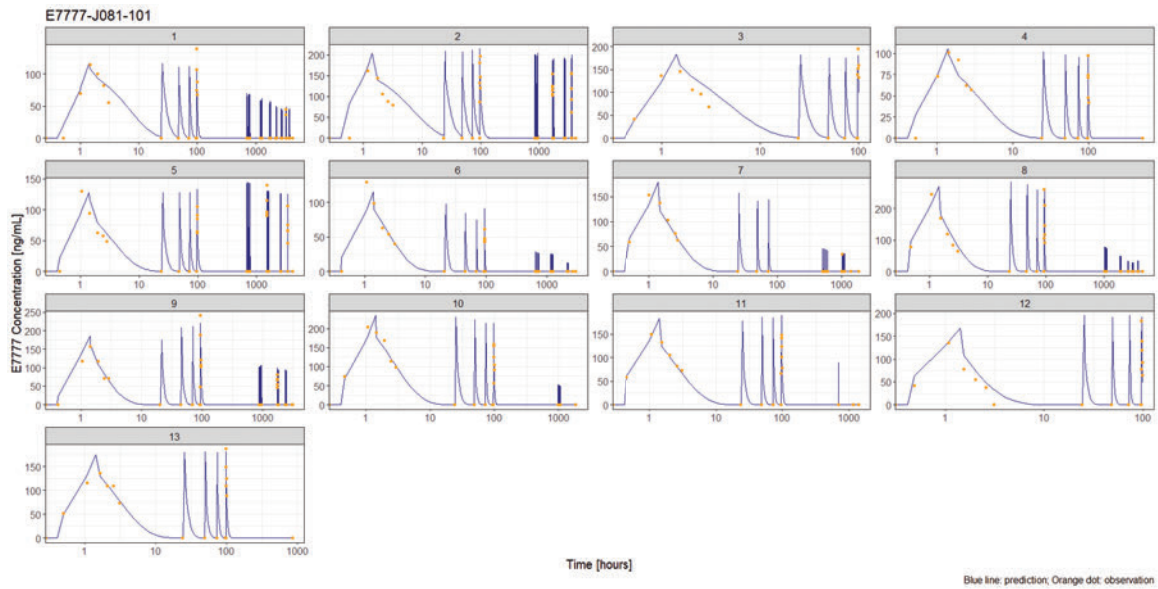
19.4.2.2.2. Objectives

- To evaluate the appropriateness of 6 mcg/kg QD for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy, (b) (4).
- To evaluate the effect of ADA on PK, efficacy, and safety of E7777.

19.4.2.2.3. Results

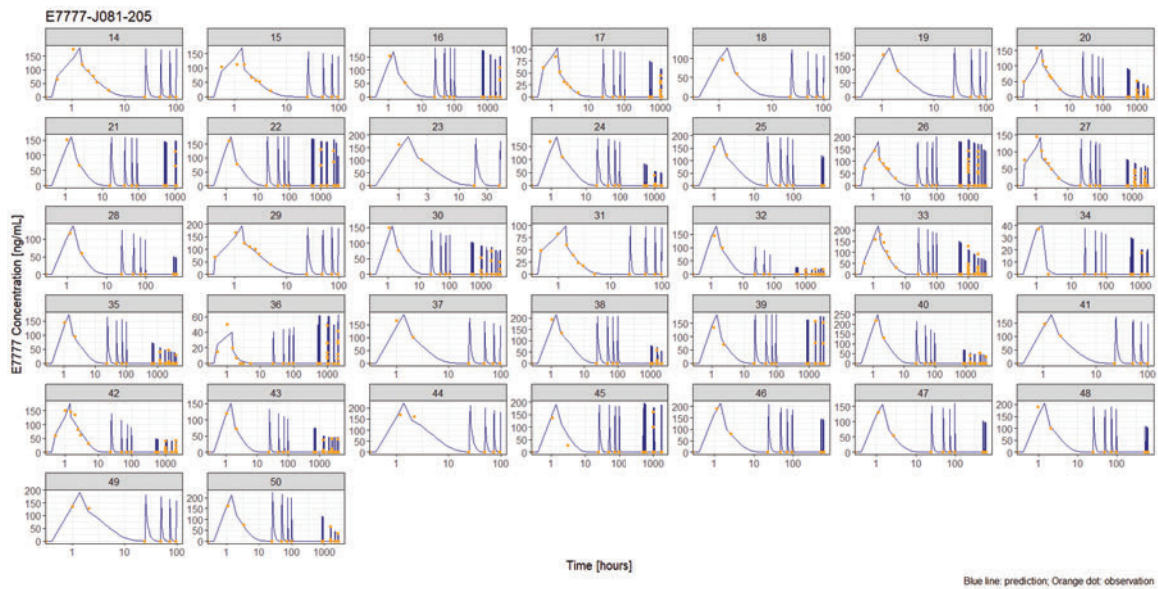
The reviewer performed independent population PK analysis. The parameter estimates were reasonably close to Applicant's. The estimated initial and steady state CL were 1.23 L/h and 8.78 L/h. Central and peripheral volume of distribution were 0.084 L and 3.49 L. Inter-compartmental CL, lag time for central compartment, and mean resident time to reach steady state CL were estimated as 8.41 L/h, 0.41 h, and 79.2 days, respectively. Figure 16 and Figure 17 show the model predictions vs. observations for all patients in Study 101 and Study 205. Figure 18 is the individual model fitting plots. It is noted the individual model prediction seems reasonable despite of relatively large eta shrinkage(eta_v1: 61.5%, eta_v2: 39.1%, eta_Q: 45.8%, eta_CLss: 57.8%, and eta_T50: 49.3%). The population PK simulations were performed with the final model to support labeling statements and exposure-response analyses as well as ADA evaluation.

Figure 16: Population PK Prediction vs. Observation for E7777-J081-101



Source: reviewer's analysis

Figure 17: Population PK Prediction vs. Observation for E7777-J081-205

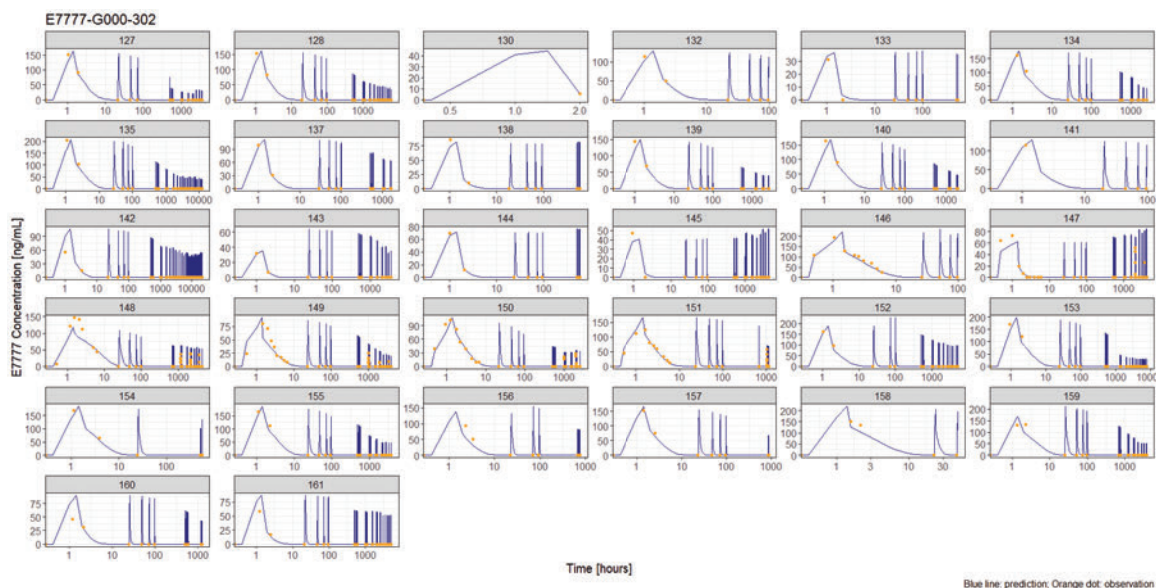


Source: reviewer's analysis

Figure 18: Population PK Prediction vs. Observation for E7777-G000-302



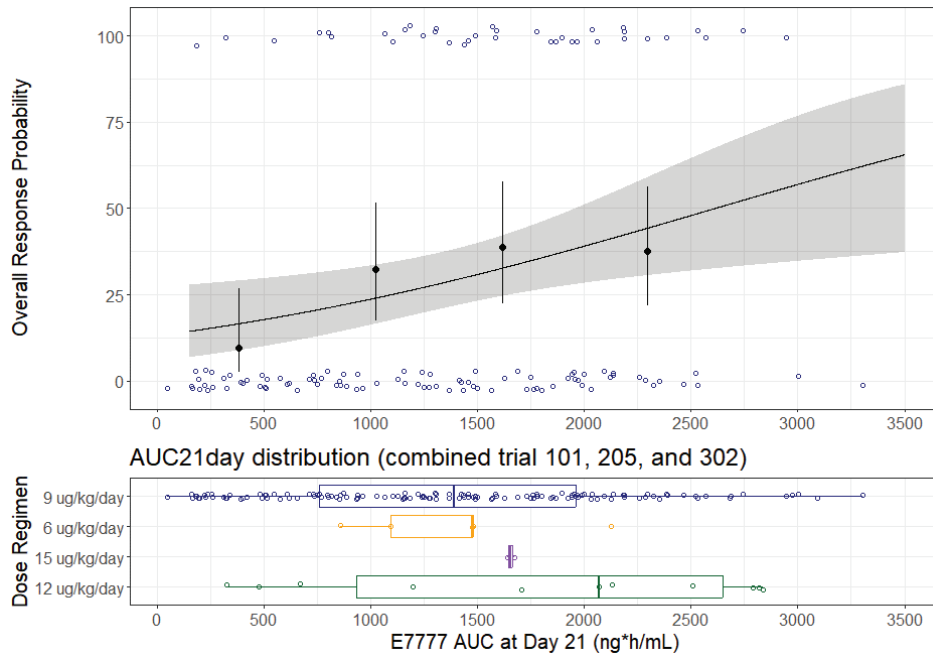
NDA/BLA Multi-disciplinary Review and Evaluation IND110489/BLA 761312
E7777 (denileukin diftitox)



Source: reviewer's analysis

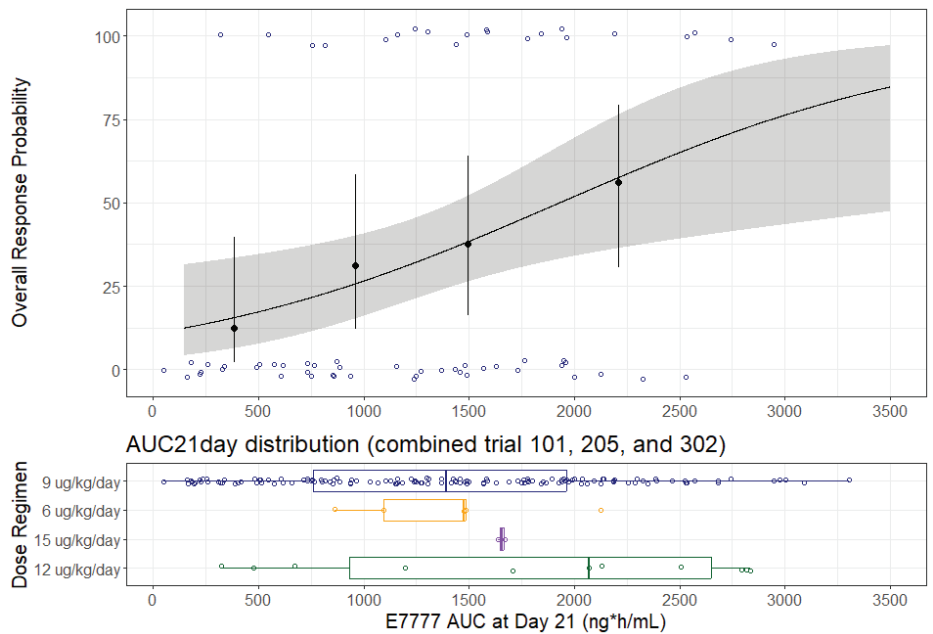
Data from 125 patients from Study 205 (N=34) and Study 302 (N=91) was used for exposure-response analysis for efficacy. Five individual PK exposure metrics, including maximum concentration within 24 hours (C_{max}24h), area under the concentration-time curve (AUC) within 24 hours (AUC_{24h}) and 21 days (AUC_{21d}) following treatment, plasma concentration at 24 hours (C_{24h}) and day 21 (C_{21d}), were estimated from final population PK model. Logistic regression was performed to explore the correlation between individual PK metrics and the efficacy endpoint ORR. Univariate analysis suggested AUC_{21d} was the only PK metrics that was statistically associated with ORR (p=0.009, Figure 19). Sensitivity analyses were performed with combined 17 CTCL patients from Study 205 and 69 patients from primary efficacy analysis dataset in Study 302 as well as with primary efficacy analysis dataset for Study 302 alone. Similar results were observed (Figure 20 for primary efficacy analysis dataset). Multivariate logistic regression confirmed the positive relationship between AUC_{21d} and ORR (p=0.014). Cancer stage (I, II, III, and IV) and best response in last treatment (CR, PD, PR, SD, and unknown/missing) were identified as covariates. These results suggest the 9 mcg/kg/day would be superior to 6 mcg/kg/day from efficacy perspective and do not support 6 mcg/kg/day.

Figure 19: Correlation Between ORR and AUC From Time 0 to 21 Days



Source: reviewer's analysis

Figure 20: Correlation Between ORR and AUC From Time 0 to 21 Days (primary efficacy analysis set)



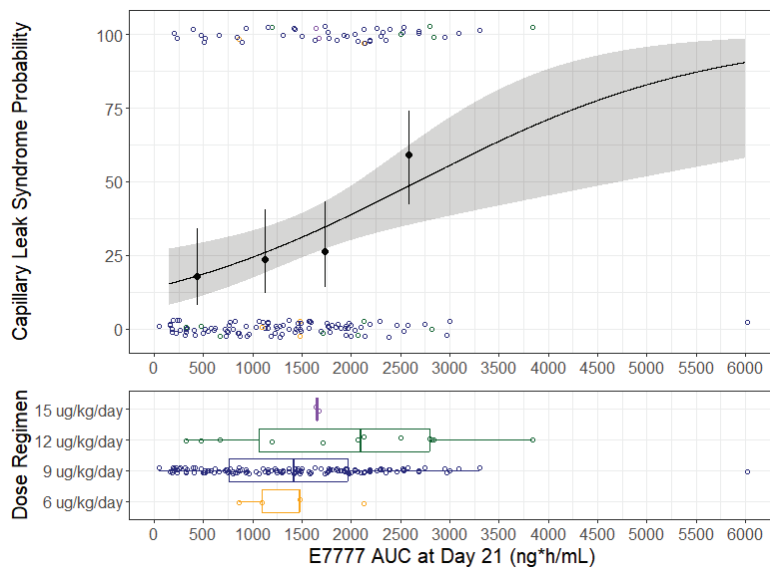
Source: reviewer's analysis

Data from 161 patients from Study 101 (N=13), 205 (N=37), and 302 (N=111) were used for exposure-response analyses for safety. Logistic regression analyses were performed to explore the correlation between the 5 individual PK exposures and the safety outcomes, including capillary leak syndrome (CLS), hepatotoxicity, visual impairment, rash, thrombotic event, infusion reaction, hypersensitivity, and infection.

The univariate analyses demonstrated that the C_{max}24h and AUC_{21d} were positively associated with CLS and hepatotoxicity, whereas the AUC_{24h} was only positively correlated with CLS ($\alpha=0.01$). AUC_{21d} showed the best correlation for both CLS and hepatotoxicity based on AIC. The increase in the AUC_{21d} leads to increased probability of CLS (Figure 21) and hepatotoxicity (Figure 22).

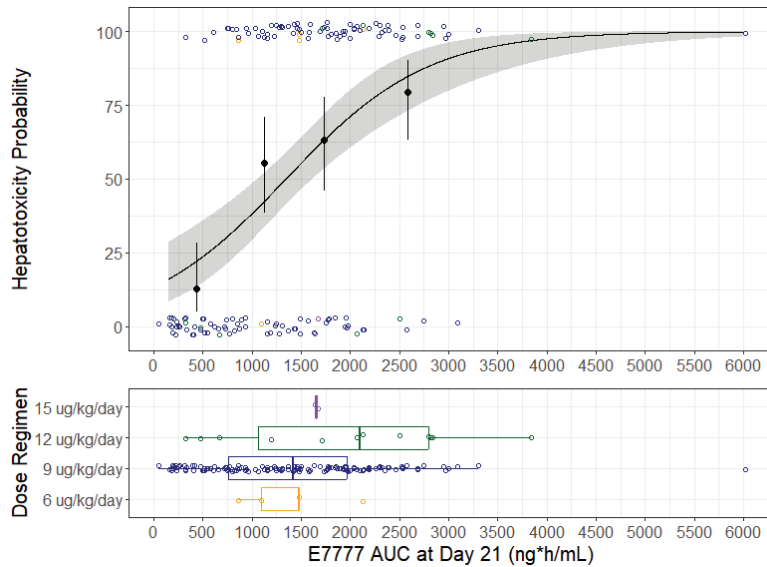
Although positive exposure-safety relationships were identified, there isn't enough information to support the 6 mcg/kg/day since 1) the number of patients with 6 mcg/kg/day was limited and 2) the 6 mcg/kg/day and 9 mcg/kg/day showed comparable PK exposures, which could result from the small sample size and large PK variability at the 6 mcg/kg/day dose level.

Figure 21: Correlation Between CLS and AUC From Time 0 to 21 Days



Source: reviewer's analysis

Figure 22: Correlation Between Hepatotoxicity and AUC from Time 0 to 21 Days



Source: reviewer's analysis

There are limitations for the exposure-response analyses for both efficacy and safety: 1) the data from dose levels other than 9 mcg/kg/day was limited; 2) unidentified covariates may exist; and 3) the measurement of serum E7777 concentration can be impacted by the presence of ADA.

During the later stages of the review cycle, it was discovered that the identified cut-off value for the ADA titer was incorrect. Due to time constraints within the current review cycle and given that the updated dataset has not been submitted at the time of review completion, the evaluation of the ADA was conducted using the dataset initially submitted for analysis. The ADA measurement method involves three types: screening, confirmatory, and titration. Screening can result in either "negative" or "potential positive" outcomes. "Negative" results in screening would not require further testing, while "potential positive" results would move on to confirmatory testing. Confirmatory testing can result in either "negative" or "positive" outcomes. Titration is observed in both screening and confirmatory testing. In the reviewer's analysis, "negative all the times" cases included those with a screening result of "negative" and those with a screening result of "potential positive" but a confirmatory result of "negative." In summary, 7 out of 37 patients from Study 205 and 5 out of 112 patients from Study 302 were negative all the times for anti-E7777 antibody. 45.9% (17/37) of patients in Study 205 and 25.0% (28/112) of patients in Study 302 were negative all the times for anti-IL2 antibody.

The ADA emerging time was accelerated around day 20 following treatment initiation (Figure 23). PK data from 8 patients in Study 205 negative for anti-E7777 antibody all the time were relatively higher than the PK observations from the patients with at least 1 observation positive

for anti-E7777 antibody (Figure 24 upper left panel red box), which implies that the anti-E7777 antibody may decrease the PK exposures of E7777.

The effect of anti-IL2 antibody on E7777 PK is inconclusive due to limited observations from patients without anti-IL2 antibody.

Figure 23: ADA Emerging Time

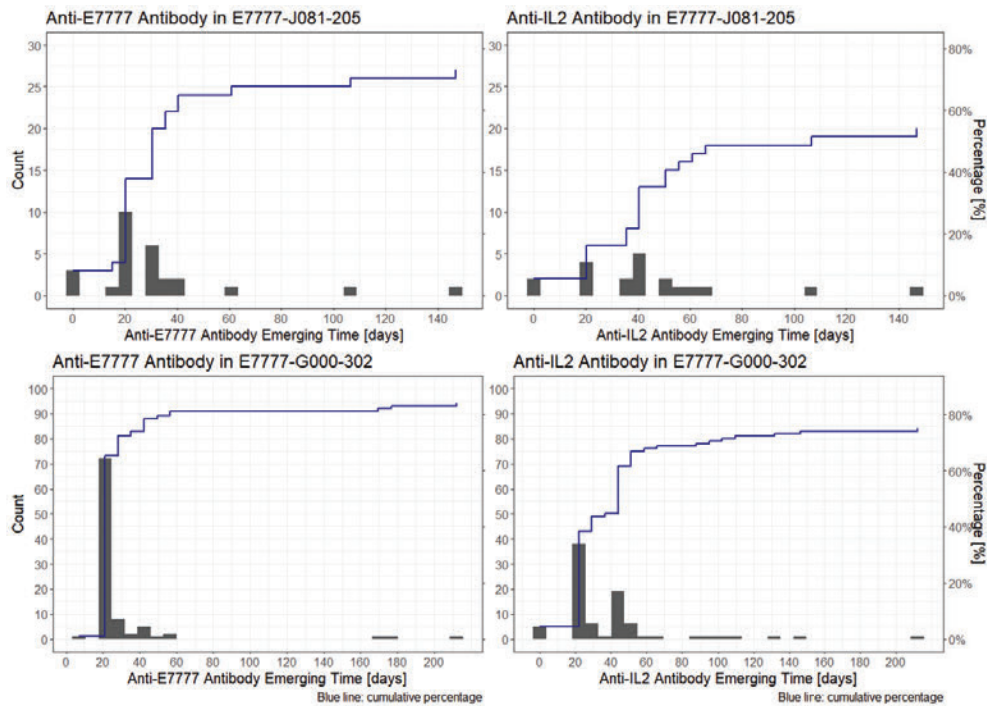
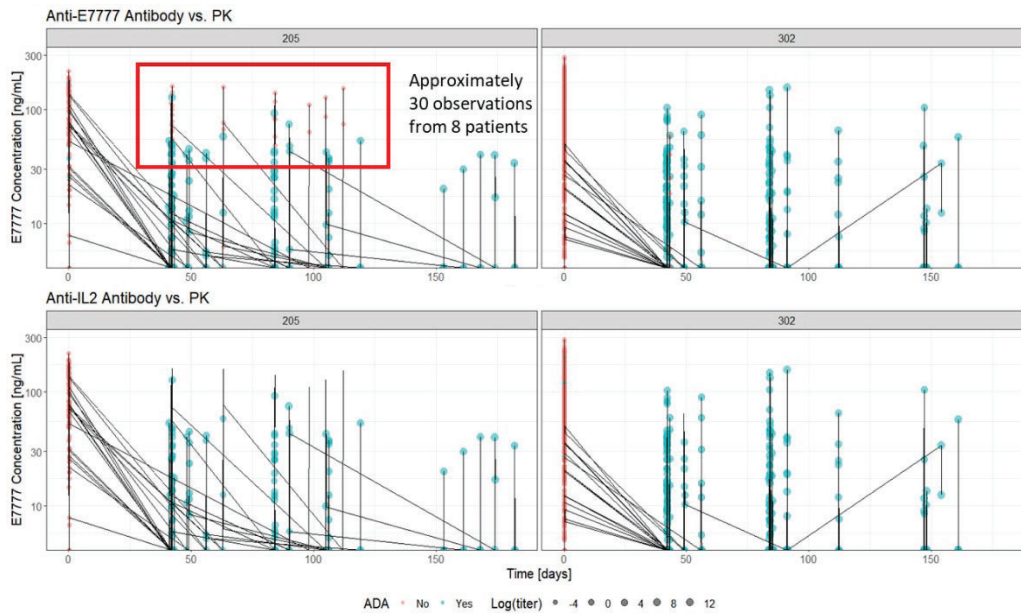


Figure 24: Individual E7777 Plasma Concentration Over Time Stratified by ADA



To evaluate the effect of ADA on efficacy and safety, logistic regressions were performed with ADA tested as binary variable (negative all the times and at least one positive observation) and numeric variable (ADA titer). For efficacy, the ADA was evaluated with AUC21d. The result suggested IL-2 antibody positive at any time and an increase in anti-IL2 antibody titer are associated with increased odds for overall response. The results should be interpreted with caution considering that unidentified confounding factors may exist and there is no clear biological rationale to support a relationship between the presence of anti-IL2 antibody and efficacy. The anti-E7777 was not significantly associated with efficacy. None of the ADA was correlated with safety outcomes ($\alpha=0.01$).

In summary, the anti-E7777 may decrease the PK exposure of E7777. There is not sufficient evidence to support the notion that ADAs affect efficacy or safety.

19.5 FDA Grouped Preferred Terms

The FDA's Assessment:

The FDA used the following grouped preferred terms in the review of safety for this application.

Table 45: FDA Grouped Preferred Terms

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", abdominal discomfort, abdominal pain upper	Abdominal distention
Anaemia	All PTs containing "anaemia"	Iron deficiency anaemia
Arthralgia	All PTs containing "arthralgia", except as noted, joint swelling, joint range of motion decreased, musculoskeletal stiffness	Back pain, bone pain, musculoskeletal pain, pain in extremity
Atrial fibrillation or flutter	All PTs containing "atrial fibrillation", "atrial flutter"	
Bruising	All PTs containing "bruise," increased tendency to bruise	Purpura
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias", all PTs containing "arrhythmia", ventricular arrhythmia, supraventricular tachycardia, supraventricular extrasystoles	Sinus bradycardia, sinus tachycardia, tachycardia
Cardiac failure	All PTs containing "cardiac failure" including cardiac failure congestive	Cardiomegaly
Chest pain	All PTs containing "chest pain", Chest discomfort, Angina pectoris	
Colitis	All PTs containing "Colitis", Enterocolitis infectious	Enterococcal gastroenteritis, gastroenteritis
Conjunctivitis	All PTs containing "Conjunctivitis"	Conjunctivitis allergic
Cough	All PTs containing "Cough", productive cough	
Cytomegalovirus infection	Cytomegalovirus infection, cytomegalovirus viraemia, cytomegalovirus test positive	Cytomegalovirus chorioretinitis
Depression	Depressed mood, depression	
Drug hypersensitivity	Drug hypersensitivity, hypersensitivity	
Dyspnoea	All PTs containing "Dyspnoea" including dyspnoea exertional	
Oedema	Oedema, oedema peripheral, generalised oedema, face oedema, swelling face, peripheral swelling,	Conjunctival oedema, ear swelling, eyelid oedema, localised

FDA Grouped PT	Included in Grouping	Not Included
		oedema, periorbital oedema
Eosinophilia	Eosinophilia, eosinophil count increased	
Fatigue	Asthenia, Fatigue, Lethargy	Malaise, muscular weakness
Fever	Pyrexia, tumour associated fever	
Gastroenteritis	Gastroenteritis, enterococcal gastroenteritis	
Headache	All PTs containing "headache", Migraine	
Haematoma	All PTs containing "haematoma", including abdominal wall haematoma	
Haemorrhage	All PTs containing "haemorrhage", "haemorrhagic", Haematuria, Epistaxis, laryngeal haemorrhage, tumour haemorrhage	Petechiae, Purpura, FDA's grouping for "Bruising"
Hepatitis	All PTs containing "hepatitis", Drug induced liver injury	FDA's "Transaminase elevation" grouping
Herpes virus infection	High-level group term, "Herpes virus infection", herpes simplex reactivation, herpes zoster	Genital herpes simplex, herpes zoster meningoencephalitis, herpes zoster oticus, ophthalmic herpes simplex, oral herpes, post herpetic neuralgia
Hyperbilirubinemia	Blood bilirubin increased	
Hyperphosphataemia	Blood phosphorus increased, hyperphosphataemia	
Hypertension	Hypertension, Blood pressure increased, hypertensive crisis	
Hypoalbuminaemia	Hypoalbuminaemia, blood albumin decreased	
Leukocytosis	Leukocytosis, White blood cell count increased	
Leukopenia	Leukopenia, White blood cell count decreased	
Lymphopenia	Lymphopenia, lymphocyte count decreased	
Lymphocytosis	Lymphocytosis, lymphocyte count increased	
Mucositis	All PTs containing mucositis, mouth ulceration, oropharyngeal pain	
Musculoskeletal pain	Back pain, Musculoskeletal pain, Neck pain, Pain in extremity, Myalgia, Bone pain, Flank pain	Arthralgia, Groin pain, tumour pain, cancer pain, muscle spasms

FDA Grouped PT	Included in Grouping	Not Included
Nail dystrophy	Nail dystrophy, nail growth abnormal	
Mental status changes	Amnesia, confusional state, delirium, altered state of consciousness, hallucinations (including auditory), memory impairment, disturbance in attention, mental status changes, somnolence, cognitive disorder	Tremor
Neutropenia	Neutropenia, Neutrophil count decreased	Febrile neutropenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, squamous cell carcinoma, Bowen's disease	
Peripheral neuropathy	Peripheral sensory neuropathy, paraesthesia, skin burning sensation, dysaesthesia	Post herpetic neuralgia, hemiparesis,
Petechiae and purpura	All PTs containing "petechiae" or "purpura"	
Pneumonia	All PTs containing "pneumonia", lower respiratory tract infection, lower respiratory tract viral infection	
Rash	All PTs containing "rash", all PTs containing "dermatitis" except as noted, Drug eruption, Erythema, Toxic skin eruption, rash maculo-papular, rash papular, rash pustular, rash pruritic, dermatitis exfoliative generalized, acute generalized exanthematous pustulosis	All PTs containing "Eczema", acarodermatitis, dermatitis contact, injection site erythema, anal erythema, vessel puncture site erythema, hyperkeratosis, dermal cyst, dermatosis, Actinic keratosis, Folliculitis, Urticaria, arthropod bite, intertrigo,
Renal insufficiency	Acute kidney injury, Blood creatinine increased, Renal impairment	
Respiratory tract infection^a	Influenza like illness	
Sepsis	All PTs containing "Sepsis", staphylococcal bacteraemia	
Skin infection	Skin infection, skin bacterial infection, staphylococcal skin infection, cellulitis, impetigo	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	
Thrombosis or thromboembolism	All PTs containing "thrombosis" (including jugular vein thrombosis, deep vein thrombosis)	
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased	PTs under FDA's "Hepatitis" grouping,

FDA Grouped PT	Included in Grouping	Not Included
		Hepatic function abnormal
Upper respiratory tract infection	All PTs containing “upper respiratory tract infection,” “sinusitis,” acute sinusitis, or “pharyngitis,” including within another word (e.g., nasopharyngitis), nasal congestion	Upper respiratory tract inflammation, laryngeal pain, pharyngeal inflammation
Urinary tract infection	All PTs containing “urinary tract infection” (including urinary tract infection bacterial), kidney infection, bacteriuria	Cystitis noninfective
Vision Changes	Vision blurred, photopsia, visual impairment	
Wound infection	Wound infection, wound infection staphylococcal	

Source: FDA analysis

^a This grouping defines respiratory tract infection (RTI) of unspecified localization. Where designated, FDA also evaluated all “RTI” including the “Upper RTI” and “Lower RTI” grouping.

Multi-Disciplinary Review Signature Page				
DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Francis Green, PharmD, MS	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature:  Francis Green -S			Digitally signed by Francis Green -S Date: 2023.07.14 16:17:40 -04'00'
Clinical Pharmacology Team Leader	Nan Zheng, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature:  Brian P. Booth -S			Digitally signed by Brian P. Booth Date: 2023.07.17 08:19:44 -04'00'
Pharmacometrics Reviewer	Ye Yuan, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature:  Ye Yuan -S			Digitally signed by Ye Yuan -S Date: 2023.07.14 16:51:44 -04'00'
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: Jiang Liu -S			Digitally signed by Jiang Liu -S Date: 2023.07.14 17:03:34 -04'00'
Pharmacogenomics Reviewer	Jeffrey Kraft, PhD	OCP/DTPM	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Jeffrey B. Kraft Jr -S			Digitally signed by Jeffrey B. Kraft Jr -S Date: 2023.07.14 17:09:57 -04'00'
Pharmacogenomics Team Leader	Sarah Dorff, PhD	OCP/DTPM	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature:  Sarah E. Dorff -S			Digitally signed by Sarah E. Dorff -S Date: 2023.07.16 22:34:37 -04'00'
Statistical Reviewer	Sarabdeep Singh, PhD	OB/DBIX	Sections: 8	Select one: ☒ Authored ☐ Approved
	Signature:  Sarabdeep Singh -S			Digitally signed by Sarabdeep Singh -S Date: 2023.07.14 12:43:11 -04'00'

Statistical Team Leader	Zhiheng Xu, PhD	OB/DBXI	Sections: 8	Select one: ☐ Authored ☒ Approved
	Signature:  Zhiheng Xu -S Digitally signed by Zhiheng Xu -S Date: 2023.07.14 14:07:13 -04'00'			
Supervisory Mathematical Statistician	Jonathon Vallejo, PhD	OOD	Sections: 8	Select one: ☐ Authored ☒ Approved
	Signature:  Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S Date: 2023.07.14 15:10:36 -04'00'			
Pharmacology/Toxicology Reviewer	Moran Choe, PhD	DHOT	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature:  Moran Choe -S Digitally signed by Moran Choe -S Date: 2023.07.13 17:39:19 -04'00'			
Pharmacology/Toxicology Team Leader (TL)	Brenda Gehrke, PhD	DHOT	Sections: 5	Select one: ☐ Authored ☒ Approved
	Signature:  Brenda Gehrke -S Digitally signed by Brenda Gehrke -S Date: 2023.07.13 18:40:00 -04'00'			
Clinical Reviewer	Shyamli Singla, MD	OOD/DHM2	Sections: All	Select one: ☒ Authored ☐ Approved
	Signature:  Shyamli Singla -S Digitally signed by Shyamli Singla -S Date: 2023.07.19 10:34:09 -04'00'			
Clinical Team Leader	Nicholas Richardson, DO, MPH	OOD/DHM2	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature:  Nicholas C. Richardson -S Digitally signed by Nicholas C. Richardson -S Date: 2023.07.27 17:14:20 -04'00'			
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	Select one: ☒ Authored ☒ Approved
	Signature:  Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2023.07.14 15:19:43 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Nicholas Richardson, DO, MPH	OOD/DHM2	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature:  Nicholas C. Richardson -S Digitally signed by Nicholas C. Richardson -S Date: 2023.07.27 17:14:44 -04'00'			
Division Director (OCP)	Brian Booth, PhD	OCP/DCP I	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature:  Brian P. Booth -S Digitally signed by Brian P. Booth -S Date: 2023.07.17 08:20:19 -04'00'			

Deputy Division Director (Acting) (Clinical)	Nicholas Richardson, DO, MPH	OOD/DHM2	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature:  Nicholas C. Richardson -S Digitally signed by Nicholas C. Richardson -S Date: 2023.07.27 17:15:13 -04'00'			
DCPI = Division of Cancer Pharmacology I				
DPM = Division of Pharmacometrics				
DTPM = Division of Translational and Precision Medicine				
DHOT = Division of Hematology, Oncology, Toxicology				
OB = Office of Biostatistics				
DBIX = Division of Biometrics IX				
OOD = Office of Oncologic Diseases				
DHM2 = Division of Hematologic Malignancies II				

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

COMPARATIVE ANALYTICAL ASSESSMENT

NDA/BLA #: BLA 761312
Supplement #:
Drug Name: Denileukin diftitox
Indication(s): For the treatment of t-cell lymphoma
Applicant: Citius Pharmaceuticals
Date(s): Review Completion Date: July 21, 2023

Review Priority: Urgent

Biometrics Division: DBVI
Statistical Reviewer: Yu-Ting Weng, Ph.D.
Concurring Reviewers: Meiyu Shen, Ph.D. and Yi Tsong, Ph.D.

Medical Division: Division of Biotechnology Review and Research IV
Pharmaceutical Quality Team: Jee Chung, Ph.D.
Project Manager: Kristine Leahy

TABLE OF CONTENTS

1 *Executive Summary* **3**
2 *Introduction*..... **4**
3 *Applicant’s Analyses and FDA Statistical Reviewer’s Comments*..... **5**
4 *Conclusion and recommendation*..... **6**
5 *References* **7**
6 *Appendix*..... **7**
6.1 *Derivation of lower confidence limit of assay screening cut point:*..... **7**

1 EXECUTIVE SUMMARY

The purpose of this review is to evaluate the applicant's statistical approach for immunogenicity assay screening cut point assessment regarding the anti-diphtheria toxin antibody.

Since nearly entire human population in the U.S. is immunized against antibody diphtheria at an early age, a wide range of polyclonal anti-diphtheria (anti-DT) antibody titers exists in normal human serum. To overcome this, the applicant diluted the human serum by a series of dilutions until the antibody level of human subject serum reached the antibody level of the rat serum. Then the applicant conducted the following analyses.

1. Titration threshold and normalization factor:

The titration threshold is the assay signal at which a sample has reached the background level of the assay. The applicant calculated the titration threshold from the dilution data of 50 human serums (each data point is the mean of dilution values by two analysts) by the Helmert transformation and Quadratic approaches that were applied to achieve the baseline signals (the steady state antibody levels) for each human serum analyzed by each analyst. The applicant claimed that they used the point estimate for 97.5th percentile as the overall assay titration threshold and calculated the assay titration threshold to be (b) (4).

Then the applicant calculated normalization factor (NF) for each plate by assay titration threshold subtracted mean response (RLU) of acceptable NC replicates, which results in NF to be (b) (4). The NF is used to determine the plate specific cut-point for all sample analysis runs.

2. Ratio screening cut point:

Applicant's screening cut point is calculated by the ratio of the mean of titers by one analyst over the mean of titers by another analyst. The applicant fit a linear mixed model with analyst as a fixed effect and sample as a random effect and selected the upper limit of the 90% confidence interval of the ratio as the 95% cut point.

We commented on the applicant's statistical approach as follows.

- 1) The applicant's 97.5th percentile calculated for the assay titration threshold ((b) (4)) is the 95% upper confidence limit for the mean of the titration data. However, the FDA guidance for industry-Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection [1] recommends 90% one-sided lower confidence limit for the 95th percentile of the treatment naïve population for screening cut point. Based on the applicant's provided titration data, the point estimate for 95th percentile is 108.69 and its 90% one-sided lower confidence limit is equal to 106.32. Refer to section 6.1 for more details.
- 2) The applicant withdrew their screening cut point for the titers after the FDA sent the following information to the applicant on June 12, 2023.

“Since the entire population has pre-existed antibody, the titers for treatment naïve human serum should be used as the screening cut point.

However, the applicant's screening cut point set by the ratio of the mean of titers by one analyst over the mean of titers by another analyst set as the screening cut point is not acceptable due to the following reasons: a) the ratio of end point titers (EPTs) of two analysts is mistakenly

interpreted as the ratio of EPT from treatment serum over EPT from treatment naïve serum; b) the analyst-to-analyst variability is already captured by the average of EPTs in titer data. c) The ratio of EPTs of post-treatment vs pre-treatment is not a correct concept for screening cut point since we can conclude that the drug is immunogenic only after post-treatment increase EPTs from pre-treatment by 19%. The guidance recommends that the cut point is the 95th percentile of naïve serum population so that false positive rate is 5%. We would not know anything about false positive rate from the ratio of EPTs of post-treatment vs pre-treatment. Most likely the false positive rate is much smaller than 5%.”

In summary, we recommend that the applicant increase the cut point for the titration data from (b) (4) to 106.32.

2 INTRODUCTION

Citius Pharmaceuticals (applicant) proposed a statistical approach to determine the immunogenicity assay screening cut point assessment regarding the anti-diphtheria toxin antibody for denileukin diftitox.

On June 1, 2023, Office of Product Quality (OPQ) requested the CMC statistical team in Office of Biostatistics (OB) to evaluate the applicant’s statistical approach for immunogenicity assay screening cut point assessment regarding the anti-diphtheria toxin antibody.

The OPQ CMC reviewer has the following question in the consultation request.

Question: From the statistical standpoint, is the applicant’s statistical approach appropriate to determine the immunogenicity assay screening cut point assessment regarding the anti-diphtheria toxin antibody for denileukin diftitox?

The FDA CMC statistical reviewers carefully evaluated the applicant’s statistical approach appropriate to determine the immunogenicity assay screening cut point assessment regarding the anti-diphtheria toxin antibody for denileukin diftitox in the BLA resubmission and noticed several issues in the applicant’s proposal.

On June 12, 2023, the FDA sent the applicant the first Information Request (IR). The request is described below.

The 1st Request 1: From the sponsor’s report (ZOW2), we understand that the titration threshold was calculated from the dilution data of 50 human serums (each data point is the mean of dilution values by two analysts) by the Helmert transformation and Quadratic approaches that were applied to achieve the baseline signals (the steady state antibody levels) for each human serum analyzed by each analyst, and the overall assay titration threshold of (b) (4) was calculated as the point estimate for 97.5th percentile. A normalization factor (NF) for each plate was established using acceptable negative control (NC) replicates, which resulted in $NF = \frac{(b) (4)}{(b) (4)}$. However, the 97.5th percentile calculated for the assay titration threshold ((b) (4)) is greater than 95.68, the estimated 95th percentile suggested in the current FDA guidance document for immunogenicity assays (Immunogenicity Testing of Therapeutic Protein Products - Developing and Validating Assays for Anti- Drug Antibody Detection). Furthermore, guidance recommends 90% one-sided lower confidence limit for 95th percentile for screening cut point. Therefore, the cut point for titration threshold would likely result in high false negative cases.

The 1st Request 2: Because the majority of the population have pre-existing antibodies to diphtheria toxin, the titers for drug naïve human serum should be used as the screening cut point. The screening cut point established by the 90% 2-sided upper confidence limit for the mean of ratio of end-point titers (EPT) by one analyst over the EPT by another analyst is not acceptable due to the following reasons: a) the ratio of EPTs of two analysts (Page 106 and Table 6 on Page 113) is mistakenly interpreted as the ratio of EPT from post-drug serum over EPT from drug naïve serum (see Page 64 of the applicant's document); b) the analyst-to-analyst variability is already captured by the average of EPTs in titer data. Furthermore, the ratio of EPTs of post-drug versus pre-drug is not appropriate for screening cut point since we conclude that the drug is immunogenic only after post-drug increase EPTs from pre-drug by 19% (1.19 ratio cut point) and this does not inform us of the false positive rate, which according to guidance should be approximately 5%.

Given request points 1 and 2 above, provide the following:

- a. Assay titration threshold value calculated according to the current recommendations in the guidance document.
- b. EPT screening cut-point from drug naïve human serum samples that allows for a 5% false positive rate.

On June 19, 2023, the applicant provided more justifications for their proposed assay screening cut point and clarified that the 1.190 ratio cut point was not utilized as the screening cut point or for EPT.

Per the applicant's justifications, we realized what the applicant calculated is not the 97.5th percentile calculated for the assay titration threshold (b) (4) but the 95% upper confidence limit for the mean of the titration data. Thus, we recalculated the estimated 95th percentile and the corresponding 90% one-sided lower confidence limit for the 95th percentile of the negative control population for screening cut point suggested in the guidance [1]. Refer to Section 6.1 for more details.

This review will evaluate the applicant's proposal. The executive summary and conclusion are summarized in Section 1 and Section 4, respectively. The applicant's analyses and our comments for the applicant's analyses are provided in Section 3.

3 APPLICANT'S ANALYSES AND FDA STATISTICAL REVIEWER'S COMMENTS

Since nearly entire human population in the U.S. is immunized against antibody diphtheria at an early age, a wide range of polyclonal anti-diphtheria (anti-DT) antibody titers exists in normal human serum. To overcome this, the applicant diluted the human serum by a series of dilutions until the antibody level of human subject serum reached the antibody level of the rat serum. Then the applicant conducted the following analyses.

1. Titration threshold and normalization factor:

The titration threshold is the assay signal at which a sample has reached the background level of the assay. The applicant calculated the titration threshold from the dilution data of 50 human serums (each data point is the mean of dilution values by two analysts) by the Helmert transformation and Quadratic approaches that were applied to achieve the baseline signals (the

steady state antibody levels) for each human serum analyzed by each analyst. The applicant used the point estimate for 97.5th percentile as the overall assay titration threshold and calculated the assay titration threshold to be (b) (4).

Then the applicant calculated normalization factor (NF) for each plate by assay titration threshold subtracted mean response (RLU) of acceptable NC replicates, which results in NF to be (b) (4). The NF is used to determine the plate specific cut-point for all sample analysis runs.

Reviewer comments: The applicant's 97.5th percentile calculated for the assay titration threshold (b) (4) is the 95% upper confidence limit for the mean of the titration data. However, the FDA guidance for industry-Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection recommends 90% one-sided lower confidence limit for the 95th percentile of the treatment naïve population for screening cut point. Based on the applicant's provided titration data, the point estimate for 95th percentile is 108.69 and its 90% one-sided lower confidence limit is equal to 106.32. Refer to section 6.1 for more details.

2. Ratio screening cut point:

Applicant's screening cut point is calculated by the ratio of the mean of titers by one analyst over the mean of titers by another analyst. The applicant fit a linear mixed model with analyst as a fixed effect and sample as a random effect and selected the upper limit of the 90% confidence interval of the ratio as the 95% cut point.

Reviewer comments: Since the entire population has pre-existed antibody, the titers for treatment naïve human serum should be used as the screening cut point.

However, the applicant's screening cut point set by the ratio of the mean of titers by one analyst over the mean of titers by another analyst set as the screening cut point is not acceptable due to the following reasons: a) the ratio of end point titers (EPTs) of two analysts is mistakenly interpreted as the ratio of EPT from treatment serum over EPT from treatment naïve serum; b) the analyst-to-analyst variability is already captured by the average of EPTs in titer data. c) The ratio of EPTs of post-treatment vs pre-treatment is not a correct concept for screening cut point since we can conclude that the drug is immunogenic only after post-treatment increase EPTs from pre-treatment by 19%. The guidance recommends that the cut point is the 95th percentile of naïve serum population so that false positive rate is 5%. We would not know anything about false positive rate from the ratio of EPTs of post-treatment vs pre-treatment. Most likely the false positive rate is much smaller than 5%.

Thus, we recommend that the applicant conduct analyses following the current recommended approaches in the guidance [1].

4 CONCLUSION AND RECOMMENDATION

We summarized our comments on the applicant's statistical approach as follows.

- 1) The applicant's 97.5th percentile calculated for the assay titration threshold (b) (4) is the 95% upper confidence limit for the mean of the titration data. However, the FDA guidance for industry-Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection [1] recommends

90% one-sided lower confidence limit for the 95th percentile of the treatment naïve population for screening cut point. Based on the applicant’s provided titration data, the point estimate for 95th percentile is 108.69 and its 90% one-sided lower confidence limit is equal to 106.32. Refer to section 6.1 for more details.

- 2) The applicant withdrew their screening cut point for the titers after the FDA sent the following information to the applicant on June 12, 2023.

“Since the entire population has pre-existed antibody, the titers for treatment naïve human serum should be used as the screening cut point.

However, the applicant’s screening cut point set by the ratio of the mean of titers by one analyst over the mean of titers by another analyst set as the screening cut point is not acceptable due to the following reasons: a) the ratio of end point titers (EPTs) of two analysts is mistakenly interpreted as the ratio of EPT from treatment serum over EPT from treatment naïve serum; b) the analyst-to-analyst variability is already captured by the average of EPTs in titer data. c) The ratio of EPTs of post-treatment vs pre-treatment is not a correct concept for screening cut point since we can conclude that the drug is immunogenic only after post-treatment increase EPTs from pre-treatment by 19%. The guidance recommends that the cut point is the 95th percentile of naïve serum population so that false positive rate is 5%. We would not know anything about false positive rate from the ratio of EPTs of post-treatment vs pre-treatment. Most likely the false positive rate is much smaller than 5%.”

In summary, we recommend that the applicant increase the cut point for the titration data from (b) (4) to 106.32.

5 REFERENCES

- [1] U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Center for Biologics Evaluation and Research. (2019). Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection.
- [2] Shen, M., X. Dong, and Y. Tsong (2015). “Statistical evaluation of several methods for cut-point determination of immunogenicity screening assay.” J Biopharm Stat 25(2): 269–279. <https://doi.org/10.1080/10543406.2014.979196>.

6 APPENDIX

6.1 Derivation of lower confidence limit of assay screening cut point:

Formulas 7 and 8 in Shen et al. (2015) [2] are defined as follows,

$$\hat{\theta}_p = \bar{X} + CZ_p S \quad (7)$$

$$\hat{\theta}_{pLB} = \hat{\theta}_p - b \sqrt{\widehat{var}(\hat{\theta}_p)} = \bar{X} + CZ_p S - b \frac{S}{\sqrt{n}} \sqrt{1 + nZ_p^2(C^2 - 1)} \quad (8)$$

Statistical Review of BLA761312

Where $\hat{\theta}_p$ is the point estimated percentile, $\hat{\theta}_{p_{LB}}$ is the $100(1 - \alpha)\%$ lower confidence bound for θ_p . p is the percentile.

C is a factor for correcting the bias of the sample standard deviation S and is defined as follows,

$$C = \sqrt{\frac{n-1}{2}} \Gamma\left(\frac{n-1}{2}\right) / \Gamma\left(\frac{n}{2}\right). \text{ n is the sample size.}$$

b is the solution of $F_{T_1}(b) = 1 - \alpha$. $\alpha \in (0,1)$. $F_{T_1}(t)$ is defined as follows.

$$F_{T_1}(t) = \int_0^\infty \Phi\left\{\sqrt{n}Z_p + \sqrt{\frac{y}{n-1}}(t\sqrt{1 + Z_p^2(C^2 - 1)} - C\sqrt{n}Z_p)\right\} \times f_{\chi^2} dy.$$

For this review, from Table 4, page 113, in the sponsor's report (ZOW2), $\bar{X} = 93.5$, $S = 9.188$, $n = 50$, $p = 0.95$, $\alpha = 0.1$, $C = 1.005$, $Z_{0.95} = 1.645$.

The solution of $F_{T_1}(b)$ can be calculated to be 1.179.

Thus, the 90% lower confidence bound for θ_p can be derived as follows.

$$\begin{aligned} \hat{\theta}_{p_{LB}} &= \hat{\theta}_p - b \sqrt{\widehat{var}(\hat{\theta}_p)} = \bar{X} + CZ_p S - b \frac{S}{\sqrt{n}} \sqrt{1 + nZ_p^2(C^2 - 1)} = 93.5 + 1.005 * 1.645 * \\ &9.188 - 1.179 * \frac{9.188}{\sqrt{50}} * \sqrt{1 + 50 * 1.645^2(1.005^2 - 1)} \sim 106.32 \end{aligned}$$

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/s/

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