

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761171Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Pharmacology/Toxicology Review

NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	BLA
Application Number(s)	761171
Priority or Standard	Priority
Submit Date(s)	March 31, 2020
Received Date(s)	March 31, 2020
PDUFA Goal Date	November 30, 2020
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	November 25, 2020
Nonproprietary Name (investigational name)	Naxitamab-gqgk (Hu3F8)
Proprietary Name	Danyelza
Pharmacologic Class	GD2-binding monoclonal antibody
Applicant	Y-mAbs Therapeutics, Inc.
Dosage Form(s) (Route(s) of administration)	Injection (for intravenous use)
Dosing Regimen	Doses of 3 mg/kg/day (up to 150 mg/day) on Days 1, 3, and 5 of each treatment cycle. Cycles repeated every 4 weeks until complete response or partial response, followed by 5 additional

{DANYELZA, naxitamab-gqgk}

	cycles every 4 weeks. Subsequent cycles may be repeated every 8 weeks until disease progression or unacceptable toxicity.
Applicant Proposed Indication(s)/Population(s)	DANYELZA is indicated for the treatment of refractory or relapsed high-risk neuroblastoma in bone ^{(b) (4)} or bone marrow in combination with GM-CSF
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	DANYELZA is a GD2-binding monoclonal antibody indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation	13
Additional Reviewers of Application.....	14
Glossary.....	15
1 Executive Summary.....	18
1.1. Product Introduction.....	18
1.2. Conclusions on the Substantial Evidence of Effectiveness	18
1.3. Benefit-Risk Assessment (BRA)	21
1.4. Patient Experience Data.....	28
2 Therapeutic Context.....	30
2.1. Analysis of Condition.....	30
2.2. Analysis of Current Treatment Options	32
3 Regulatory Background	33
3.1. U.S. Regulatory Actions and Marketing History.....	33
3.2. Summary of Presubmission/Submission Regulatory Activity	33
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	37
4.1. Office of Scientific Investigations (OSI)	37
4.2 Product Quality	38
4.3. Clinical Microbiology	38
4.4. Devices and Companion Diagnostic Issues	38
5 Nonclinical Pharmacology/Toxicology.....	39
5.1. Executive Summary	39
5.2. Referenced NDAs, BLAs, DMFs.....	42
5.3. Pharmacology.....	42
5.4. ADME/PK	52
5.5. Toxicology.....	56

5.5.1. General Toxicology.....	56
5.5.2. Genetic Toxicology.....	65
5.5.3. Carcinogenicity.....	66
5.5.4. Reproductive and Developmental Toxicology.....	66
5.5.5. Other Toxicology Studies.....	67
6 Clinical Pharmacology.....	68
6.1. Executive Summary.....	68
6.2. Summary of Clinical Pharmacology Assessment.....	69
6.2.1. Pharmacology and Clinical Pharmacokinetics.....	69
6.2.2. General Dosing and Therapeutic Individualization.....	69
6.2.2.1. General Dosing.....	69
6.2.2.2. Therapeutic Individualization.....	70
6.2.2.3. Outstanding Issues.....	70
6.3. Comprehensive Clinical Pharmacology Review.....	71
6.3.1. General Pharmacology and Pharmacokinetic Characteristics.....	71
6.3.2. Clinical Pharmacology Questions.....	72
7 Sources of Clinical Data.....	76
7.1. Table of Clinical Trials.....	76
8 Statistical and Clinical Evaluation.....	80
8.1. Review of Relevant Individual Trials Used to Support Efficacy.....	80
8.1.1. Trial 12-230.....	80
8.1.2. Trial Results.....	89
8.1.3. Trial 201.....	110
8.1.4. Trial Results.....	116
8.1.5. Retrospective Study 2PR01.....	139
8.1.6. Study Results.....	142
8.1.7. Integrated Review of Effectiveness.....	147
8.1.8. Assessment of Efficacy Across Trials.....	148

8.1.9. Integrated Assessment of Effectiveness	150
8.2. Review of Safety	153
8.2.1. Safety Review Approach	154
8.2.2. Review of the Safety Database	155
8.2.3. Adequacy of Applicant’s Clinical Safety Assessments	163
8.2.4. Safety Results	165
8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability	207
8.2.6. Safety Analyses by Demographic Subgroups	207
8.2.7. Analysis of Submission-Specific Safety Issues	213
8.2.8. Specific Safety Studies/Clinical Trials	227
8.2.9. Additional Safety Explorations	227
8.2.10. Safety in the Postmarket Setting	229
8.2.11. Integrated Assessment of Safety	230
SUMMARY AND CONCLUSIONS	235
8.3. Statistical Issues	235
8.4. Conclusions and Recommendations	235
9 Advisory Committee Meeting and Other External Consultations	241
10 Pediatrics	242
11 Labeling Recommendations	243
12 Risk Evaluation and Mitigation Strategies (REMS)	251
13 Postmarketing Requirements and Commitment	252
14 Division Director (DHOT) (NME ONLY)	256
15 Division Director (OCP)	257
16 Division Director (OB)	258
17 Acting Deputy Division Director (Clinical)	259

{DANYELZA, naxitamab-gqgk}

18	Office Director (or designated signatory authority)	260
19	Appendices	261
19.1.	References	261
19.2.	Financial Disclosure	263
19.3.	Nonclinical Pharmacology/Toxicology.....	270
19.4.	OCP Appendices (Technical documents supporting OCP recommendations)	270
19.5.	Additional Safety Analyses Conducted by FDA	291

Table of Tables

Table 3-1. Key Regulatory History - IND 132793	34
Table 5-1: Binding affinity of humanized and chimeric anti-GD2 antibodies for human GD2.....	43
Table 5-2: ADCC and CDC activity of naxitamab compared to m3F8 and 14.G2a.....	44
Table 5-3: ADCC and CDC activity against neuroblastoma cell lines	44
Table 5-4: GM-CSF enhancement of m3F8-mediated ADCC by PMNs against LAN-1 and NMB7 cells	45
Table 5-5: m3F8-mediated ADCC using PMN as effector cells	46
Table 5-6: Naxitamab binding to rat and human target cells.....	47
Table 5-7: Percent Naxitamab-Mediated Cytotoxicity by Nude Rat Splenocytes against Rat or Human Cells.....	47
Table 5-8: Percent naxitamab-induced ADCC using human effector and target cells	48
Table 5-9: Improved limb weakness in rats with epidural neuroblastoma treated with m3F8...	49
Table 5-10: Percent maximum allodynia in adult SD rats.....	51
Table 6-1. Summary of simulated naxitamab clearance and AUC _{0-672h} versus bodyweight	73
Table 7-1-1 Listing of Clinical Trials Relevant to Naxitamab BLA.....	77
Table 8-1: Patients Excluded from 12-230 Efficacy Population due to Receipt of Radiation to Target Lesions	88
Table 8-2 Summary of Enrollment and Disposition, Trial 12-230.....	90
Table 8-3: Responding Patients with Baseline Disease Assessments Less than Four Weeks from Prior Systemic Therapy in Trial 12-230	93
Table 8-4: Demographics and Baseline Characteristics of Primary Efficacy Population (N = 38), Trial 12-230	95

Table 8-5: Patients in Trial 12-230 Efficacy Population who Received Radiation Prior to Onset of an Objective Response	98
Table 8-6: Overall Response Rate in the Primary Efficacy Population, Trial 12-230	102
Table 8-7: Summary of ORR Subgroup Analyses by Demographic Characteristics, Trial 12-230	106
Table 8-8: Overall Response Rate Subgroups by Anti-GD2 Exposure and Baseline Disease Status in Trial 12- 230	107
Table 8-9: Summary of Duration of Response, Trial 12-230.....	108
Table 8-10 Summary of Enrollment and Disposition, Trial 201 Safety Analysis Set.....	117
Table 8-11 Summary of Baseline Demographics, Trial 201, Cohort 1 FAS	119
Table 8-12: Responding Patients with Baseline Disease Assessments Less than Four Weeks from Prior Systemic Therapy in Trial 201	121
Table 8-13 Summary of Overall Response Rate, Trial 201.....	126
Table 8-14 Summary of ORR Subgroup Analyses by Demographic Characteristics, Trial 201 ...	132
Table 8-15: Overall Response Rate Subgroups by Anti-GD2 Exposure and Baseline Disease Status in Trial 201.....	132
Table 8-16 Summary of Duration of Response, Trial 201	133
Table 8-17: Summary of Duration of Response Data including Assessments after End of Treatment (Data cut-off 7/23/2020)	134
Table 8-18 Summary of Efficacy Analysis for 2PR01, Pooled Categories 1 and 2, Full Analysis Set	145
Table 8-19 Summary of Efficacy Analysis for 2PR01, Category 3, Full Analysis Set	145
Table 8-20: GM-CSF Enhancement of mu3F8–Mediated Granulocyte ADCC	148
Table 8-21 Demographics and Baseline Characteristics – Trials 12-230, 201, and 2PR01 (SAF)	158

Table 8-22: Demographics and Baseline Characteristics – Trials 12-230, 201, and 2PR01 (Unique Subjects in SAF) (Applicant’s Analysis)	159
Table 8-23: Summary of Demographics and Baseline Characteristics, Trial 12-230, Patients who Received 3 mg/kg (Applicant’s Analysis)	161
Table 8-24 Summary of Treatment-related ^a SAEs Reported for Trial 12-230, Trial 201, and Retrospective Trial 2PR01 (SAF).....	166
Table 8-25: Summary of Serious Treatment Emergent Adverse Events Reported in at Least 2 Subjects by System Organ Class and Preferred Term Corresponding Serious, Treatment-Related Adverse Events Trial 12-230 Phase 1 and 2 Subjects with Dose of 3mg/kg (Safety Analysis Set) (Applicant’s Analysis).....	168
Table 8-26: Summary of SAEs and Treatment-related SAEs Reported for Trial 12-230 Subjects, Trial 201 Subjects, and Retrospective Study 2PR01 Patients (Applicant’s Analysis)	170
Table 8-27: Selected Serious Adverse Event Narratives from Trials 12-203 and 201	172
Table 8-28: Serious Adverse Events in Trial 201: 120-day Safety Update	181
Table 8-29: Serious Adverse Events in Trial 12-230: 120-Day Safety Update	182
Table 8-30: Discontinuations due to Adverse Events, Trial 12-230*	184
Table 8-31: Adverse Events Leading to Treatment Interruption in Trial 12-230.....	185
Table 8-32: Adverse Events Leading to Treatment Interruption in Trial 201	186
Table 8-33 Summary of Treatment-Related Treatment-Emergent Adverse Events Reported for at least 10% of Trial 12-230 Subjects in the Safety Analysis Set...	188
Table 8-34 Summary of Treatment-related Treatment-Emergent Adverse Events Experienced by at least 10% of Trial 201 Subjects	189
Table 8-35: Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term Corresponding Treatment-Related Adverse Events, Grade 3 or Higher, and Treatment-Related Grade 3 or Higher Trial 12-230 Phase 1 and 2 Subjects with Dose of 3mg/kg (Safety Analysis Set) (Applicant’s Analysis)	193

{DANYELZA, naxitamab-gqgk}

Table 8-36: Summary of Treatment Emergent Adverse Events Reported by at least 10% of Subjects in Trial 201, Corresponding Treatment-related Adverse Events, Grade 3 or Higher and Treatment-related Grade 3 or Higher Adverse Events (Applicant's Analysis)	195
Table 8-37 Summary of Treatment Emergent Adverse Events Grade 3 and Higher Reported in at least 10% of Subjects by Study (Safety Analysis Set) (Applicant's Analysis)	197
Table 8-38: Corresponding Treatment-Related Grade 3 or Higher Trial 12-230 Phase 1 and 2 Subjects with Dose of 3mg/kg (Safety Analysis Set) (Applicant's Analysis)	199
Table 8-39 : Summary of Treatment Emergent Abnormal Laboratory Values by Highest CTCAE Grade Worsening from Baseline in Trial 201 (Applicant's Analysis).....	201
Table 8-40: Laboratory Abnormalities (>20%) That Worsened from Baseline in Trial 201 (FDA Analysis)	202
Table 8-41: Laboratory Abnormalities in Patients who Received the RP2D of Naxitamab in Trial 12-230, Worsening from Baseline Analysis (FDA Analysis)	203
Table 8-42: Patients with QT Prolongation in Trial 12-230	205
Table 8-43: Summary of Subjects by Adverse Event Category by Sex (Trial 12-230 Safety Analysis Set) (Applicant's Analysis).....	208
Table 8-44: Summary of Subjects by Adverse Event Category by Sex (Trial 201 Safety Analysis Set) (Applicant's Analysis).....	209
Table 8-45: Summary of Subjects by Adverse Event Category by Age Group (Trial 12-230 Safety Analysis Set) (Applicant's Analysis).....	210
Table 8-46: Summary of Subjects by Adverse Event Category by Age Group (Trial 201 Safety Analysis Set) (Applicant's Analysis).....	210
Table 8-47 : Summary of Subjects by Adverse Event Category by Race (Trial 12-230 Safety Analysis Set) (Applicant's Analysis).....	211
Table 8-48: Summary of Subjects by Adverse Event Category by Race (Trial 201 Safety Analysis Set) (Applicant's Analysis).....	212

Table 19-1	Summary of Disclosable Financial Arrangements and Interest.....	263
Table 19-2:	FDA Analysis of Disclosable Financial Interests	264
Table 19-3.	Overview of studies included in the population PK analysis.	271
Table 19-4.	Summary of Demographics.....	272
Table 19-5.	Parameter estimates of the final population PK model	274
Table 19-6.	Summary of simulated naxitamab clearance and AUC _{0-672h} versus bodyweight. ...	278
Table 19-7.	Summary of simulated naxitamab C _{max} on Day 1, Day 3 and Day 5 versus bodyweight group	279
Table 19-8.	Overview of number of patients with ADA formation by trial	280
Table 19-9.	Summary of overall and complete response rates.....	283
Table 19-10.	Occurrence of grade 2+ bronchospasm, hypertension and hypotension events stratified by covariates of interest.....	285

Table of Figures

Figure 1:	m3F8-mediated ADCC by PMNs against NMB7 cells.....	45
Figure 2:	Time course of GM-CSF increase in ADCC of NMB7 cells by m3F8	45
Figure 3:	Naxitamab-induced ADCC using human LAN-1 or IMR-32 cells and human NK cells ...	48
Figure 4:	Anti-tumor activity of naxitamab and m3F8 in adult mice bearing subcutaneous LAN-1 tumors	49
Figure 5:	Mechanical threshold for withdrawal in rats treated with an anti-GD2 antibody.....	50
Figure 6:	Thermal latency in rats administered intravenous or intrathecal anti-GD2 antibody ..	50

Figure 7: Single IV administration of ch14.18 led to lower mechanical pain threshold in adult SD rats.....	51
Figure 8-1 Basic Trial Design	81
Figure 19-1. Diagnostic plots for the final population PK model.....	274
Figure 19-2. Visual predictive check stratified by trial for final population PK model	276
Figure 19-3. Simulated naxitamab clearance and AUC _{0-672h} versus body weight.....	277
Figure 19-4. Simulated naxitamab C _{max} on Day 1, Day 3 and Day 5 versus bodyweight group .	278
Figure 19-5. Naxitamab concentration in patients with and without ADA formation in Trial 201	281
Figure 19-6. Simulated naxitamab exposures versus bodyweight with dosing cap of 450 mg per cycle.	282
Figure 19-7. Logistic regression analysis of exposures of naxitamab for ORR or CR.....	284
Figure 19-8. Observed and predicted incidence rate of grade 2+ hypertension events versus naxitamab exposure AUC _{24h}	286
Figure 19-9. Observed and predicted incidence rate of grade 2+ hypotension events versus naxitamab exposure AUC _{24h}	287
Figure 19-10. Grade 2+ bronchospasm stratified by prior Anti-GD2 treatment.	288
Figure 19-11. Logistic regression of grade 2+ bronchospasm with naxitamab exposure (AUC _{24h})	288
Figure 19-12. Logistic regression of Grade 2+ hypotension with naxitamab exposure (AUC _{24h}) in Study 11-009, 12-116 and 12-230	289
Figure 19-13. Grade 2+ hypotension stratified by prior Anti-GD2 treatment.....	289
Figure 19-14. Grade 3 hypotension stratified by study	290
Figure 19-15. Logistic regression of Grade 3 hypotension with naxitamab exposure (AUC _{24h}).	290

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Rebecca Cohen
Pharmacology/Toxicology Reviewer(s)	Stephanie Aungst
Pharmacology/Toxicology Supervisor	Whitney Helms
Office of Clinical Pharmacology Reviewer(s)	Catharine Bulik
Office of Clinical Pharmacology Team Leader(s)	Hong Zhao
Clinical Reviewer	Diana Bradford
Clinical Team Leader	Amy Barone
Safety Analyst (if applicable)	Min Wang, Yutao Gong
Statistical Reviewer	Xiaoxue Li
Statistical Team Leader	Pallavi Mishra-Kalyani
Cross-Disciplinary Team Leader	Amy Barone
Division Director (DHOT)	John Leighton
Division Director (OCP)	Nam Atiqur Rahman
Division Director (OB)	Shenghui Tang
Acting Deputy Division Director (OOD)	Martha Donoghue
Office Director (or designated signatory authority)	Marc Theoret

Additional Reviewers of Application

OPQ	Ian McWilliams/ Brian Roelofs/Will Hallett (OBP Application Technical Lead) OBP Labeling: Vicky Borders-Hemphill
Microbiology	OPM DS Facility, Micro & Process: Viviana Matta/ Max Van Tassell OPMA DP Facility, Micro and Process : Yun Wy/Virginia Carroll OPMA DP/DS Ladership: Maria CandauChaon (TL), Zhihao (Peter Qiu)
OPDP	Robert Nguyen
OSI	Michelle Fedowitz/Karen Bleich (TL)
OSE/DEPI	DEPI: Fang Tian/ Scott Swain DPV: Michelle Nadeau-Nguyen/ Peter Waldron/ Afrouz Nayernama
OSE/DMEPA	Janine Stewart/ Alice Tu
OSE/DRISK	Naomi Boston
Other	OOD Safety: Shanthi Marur/Meredith Chuk Patient Labeling Team: Jessica Chung/Barbara Fuller (TL)

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADA	antidrug antibodies
ADCC	antibody-dependent cellular cytotoxicity
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AUC	area under the concentration time curve
AUC _{0-48.5h}	area under the concentration time curve from beginning of a naxitamab infusion to 48 h after the infusion ends
AUC _{0-216h}	area under the concentration versus time curve from Time 0 to 216 hours
AUC _{0-∞}	area under the concentration time curve from Time 0 to infinity
BLA	biologics license application
CD	cluster of differentiation
CD16	FcγRIIIa
CD32	FcγRIIa
CDC	complement-dependent cytotoxicity
CDR	complementarity-determining region
CFR	Code of Federal Regulations
CL	clearance
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CV	coefficient of variation
DoR	duration of response
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
GM-CSF	granulocyte-macrophage colony-stimulating factor

{DANYELZA, naxitamab-gqgk}

hu3F8	humanized 3F8 monoclonal antibody
Ig	immunoglobulin
IL-2	interleukin-2
ICH	International Council for Harmonisation
IND	Investigational New Drug
INRC	International Neuroblastoma Response Criteria
INRG	International Neuroblastoma Risk Group Classification system
i.v.	intravenous
mAB	monoclonal antibody
max	maximum
min	minimum
MRD	minimum residual disease
MSK	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
mu3F8	murine 3F8 monoclonal antibody
MYCN	Myelocytomatosis Viral-Related Oncogene, Neuroblastoma derived
NB	neuroblastoma
NC	not calculated
NE	not estimable
No.	number
NOAEL	no observed adverse effect level
OR	objective response
ORR	overall response rate
OS	overall survival
PAS	primary analysis set
PD	progressive disease
PFS	progression free survival
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

{DANYELZA, naxitamab-gqgk}

OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PP	per protocol
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
qPCR	quantitative PCR
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SCT	stem cell transplant
SD	standard deviation
SOC	standard of care
$t_{1/2}$	terminal half-life
TEAE	treatment emergent adverse event
T_{max}	time to reach maximum plasma concentration
V_1	central volume of distribution
Y-mAbs	Y-mAbs Therapeutics, Inc.

1 Executive Summary

1.1. Product Introduction

On March 31, 2020, Y-mAbs Therapeutics, Inc. (Y-mAbs) submitted original Biologics License Application (BLA) under Section 351(a) of the Public Health Service Act seeking approval of naxitamab-gqgk (Danyelza) for the treatment of patients with refractory or relapsed high-risk neuroblastoma in bone or bone marrow in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF).

Naxitamab-gqgk (naxitamab, hu3F8-IgG1; will be referred to as naxitamab for the remainder of this document) is a humanized IgG1 monoclonal antibody directed against the glycolipid disialoganglioside (GD2), which is a member of the b-series gangliosides and an adhesion molecule widely expressed on the cell membrane in neuroectoderm-derived tumors; the established pharmacological class is GD2-binding monoclonal antibody. In vitro, naxitamab was shown to bind to cell surface GD2 and induce complement-dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC). Naxitamab contains human framework regions and murine complementarity-determining regions. Naxitamab is produced from a Chinese hamster ovary cell line and has an approximate molecular weight of 144 kDa without glycosylation. Naxitamab injection is supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution for intravenous infusion. Each single-dose vial contains 40 mg of naxitamab in 10 mL of solution. Each mL of solution contains 4 mg of naxitamab and citric acid anhydrous (0.71 mg), poloxamer 188 (1.5 mg), sodium chloride (7.01 mg), sodium citrate (6.3 mg), and Water for Injection, USP. The pH is approximately 5.7. Although the two trials supporting efficacy and safety in this application used different manufacturing processes, OBP determined that the products used in each trial were generally comparable. Naxitamab is a new molecular entity and has not been previously marketed in the U.S. or approved for any indication by FDA or globally.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The recommendation for accelerated approval is based on the results from two single-arm, open-label trials: Trial 201 (NCT 03363373) and Trial 12-230 (NCT 01757626).

Both trials enrolled patients with relapsed or refractory high risk neuroblastoma in the bone or bone marrow who had demonstrated a response of minor response, partial response, or stable disease to prior therapy. Patients received naxitamab 9 mg/kg/cycle administered as three

{DANYELZA, naxitamab-gqgk}

separate intravenous infusions of 3 mg/kg (on Days 1, 3 and 5) in the first week of each cycle. Patients received GM-CSF subcutaneously at 250 µg/m²/day on Days -4 to 0 and at 500 µg/m²/day on Days 1 to 5. The primary efficacy population included patients with relapsed or refractory disease in the bone or bone marrow who had demonstrated a response of stable disease or better in response to prior therapy, had evaluable disease per blinded independent central review according to the revised International Neuroblastoma Response Criteria (INRC), and who received at least one dose of naxitamab. The primary efficacy population was comprised of 22 patients in Trial 201 and 39 patients in Trial 12-230.

The analysis of efficacy demonstrated a clinically meaningful overall response rate (ORR) per independent review with sufficient duration to represent a clinically meaningful treatment effect in pediatric patients with relapsed and refractory neuroblastoma with disease in the bone or bone marrow. Patients in both trials were permitted to receive radiation in certain circumstances, although assessment of response excluded sites that received radiation. Patients for whom radiation was administered to the only site of evaluable disease, which applied only to patients in Trial 12-230, were excluded from the efficacy analysis. Patients with a best response of progressive disease to initial therapy or therapy at relapse were excluded from Trial 201 and from the efficacy analysis population in Trial 12-230. Therefore, the indication the review team proposes for approval also excludes these patients.

In Trial 201 (n=22), the confirmed ORR in patients with metastatic, relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who demonstrated a response of stable disease, partial response, or minor response to prior therapy per blinded, independent review was 45% (95% CI: 24%, 68%), with 30% of the 10 responders having observed duration of response (DOR) of at least 6 months. The primary efficacy analysis in Trial 201 included 4 patients with prior anti-GD2 treatment; one (25%) of these patients demonstrated a response.

In Trial 12-230 (n=38), the confirmed ORR per blinded, independent review according to the revised INRC was 34% (95% CI: 20%, 51%), with 23% of the 13 responders having an observed DOR of 6 months. The primary efficacy analysis in Trial 12-230 included 22 patients with prior anti-GD2 treatment; 4 (18%) of these patients demonstrated a response (95% CI 5%, 40%). Given the limited number of patients with prior anti-GD2 exposure, the exploratory analyses of ORR in this subpopulation should be interpreted with caution; however, the results suggest that naxitamab has clinical activity in patients who received prior anti-GD2 antibody therapy. The difference in the point estimates of ORR between the two trials may be explained by the higher percentage of relapsed patients, who are more heavily pre-treated, in Trial 12-230 (55% vs. 36% in Trial 201).

{DANYELZA, naxitamab-gqgk}

Assessment of DOR was limited by administration of additional anticancer therapies subsequent to achieving a complete or partial response in patients in both trials. Neither study was designed to include scheduled assessments of response after completion of treatment with naxitamab, and Trial 201 is currently ongoing. Additional clinical data from Trial 201 may provide additional data to inform durability of responses.

Given the rarity of relapsed or refractory high-risk neuroblastoma and the lack of an approved or standard treatment, a randomized trial is not likely to be feasible in this population. The review team considers that the observed ORR in the two trials, along with the DOR, in patients treated with naxitamab in combination with GM-CSF sufficient to provide substantial evidence of the effectiveness of naxitamab in the rare population of patients with relapsed or refractory neuroblastoma who have disease in the bone or bone marrow. In vitro data demonstrating ADCC with the monoclonal antibody mu3F8 (a previously studied, murine form of naxitamab) was provided to support the contribution of effect of GM-CSF. Dose-dependent ADCC was demonstrated with m3F8, while adding GM-CSF resulted in a reduction in concentration of mu3F8 required to mediate ADCC. Data from additional patients in this patient population, including ORR and DOR obtained from a broad representation of clinical sites, may be required to confirm clinical benefit.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Efficacy: The effectiveness of naxitamab for the treatment of relapsed or refractory high-risk neuroblastoma with bone or bone marrow involvement was established based on data from 38 patients in Trial-230 and 22 patients in Trial 201. Both trials enrolled patients 1 year of age and older with primary refractory disease or incomplete response to salvage treatment in the bone or bone marrow. In Trial 201, the confirmed ORR per blinded, independent review was 45% (95% CI: 24%, 68%), with 30% of the 10 responders having an observed DOR of at least 6 months. The primary efficacy analysis in Trial 201 included 4 patients with prior anti-GD2 treatment, and 1 (25%) of these patients demonstrated a response. In Trial 12-230, the confirmed ORR per blinded, independent review according to the revised International Neuroblastoma Response Criteria (INRC) was 34% (95% CI: 20%, 51%), with 23% of the 13 responders having an observed DOR of 6 months. The primary efficacy analysis in Trial 12-230 included 22 patients with prior anti-GD2 treatment, and 4 (18%) of these patients demonstrated a response (95% CI 5%, 40%). Given the limited number of patients with prior anti-GD2 exposure, the exploratory analyses of ORR in this subpopulation should be interpreted with caution; however, the results suggest that naxitamab has some clinical activity in patients with prior anti-GD2 antibody exposure. The difference in the point estimates of ORR between the two trials may be explained by the higher percentage of relapsed patients, who are more heavily pre-treated, in Trial 12-230.

Assessment of DOR was limited by administration of additional anticancer therapies subsequent to achieving a complete or partial response in patients in both trials. Neither study was designed to include scheduled assessments of response after completion of treatment with naxitamab, and Trial 201 is currently ongoing. Additional clinical data from Trial 201 may provide additional data to inform durability of responses.

Although the investigational naxitamab used in the two trials supporting efficacy and safety in this application used different manufacturing processes, the Office of Biotechnology Products (OBP) determined that the products used in each trial were generally comparable, although

direct comparability of potency was not possible given differences in potency assays used for each product (refer to page 32 of the OBP assessment for details).

Safety: The safety of naxitamab in combination with GM-CSF was evaluated in a subpopulation of patients with relapsed or refractory neuroblastoma high-risk neuroblastoma in bone or bone marrow, from two open-label, single arm studies, Study 201 (n=25) and Study 12-230 (n=72). In both studies, patients received naxitamab as three separate intravenous infusions of 3 mg/kg (Days 1,3 and 5) in the first week of a 4-week cycle. Patients also received GM-CSF subcutaneously at 250 µg/m²/day on Days -4 to 0 and at 500 µg/m²/day on Days 1 to 5. No deaths due to an adverse event were reported. Cumulative safety data indicated that serious adverse reactions occurred in 32% of patients in Trial 201 and 40% of patients in Trial 12-230. Serious adverse reactions occurring in > 5% of patients in Trial 201 included anaphylactic reaction (12%) and pain (8%); in Trial 12-230 serious adverse reactions occurring in >5% of patients included hypertension (14%), hypotension (11%), and pyrexia (8%).

Naxitamab can cause serious infusion-related reactions and neurologic toxicity, including severe pain, transverse myelitis and reversible posterior encephalopathy syndrome (RPLS). Given the potential severity of these adverse reactions and the occurrence of infusion related reactions and pain in most patients in both trials, a boxed warning was included in Danyelza product labelling for both infusion reactions and neurotoxicity. FDA's pooled term analysis of infusion-related reactions included the following terms: hypotension, bronchospasm, flushing, wheezing, stridor, urticaria, dyspnea, pyrexia, infusion related reaction, face edema, swelling face, orbital edema, periorbital edema, lip edema, lip swelling, mouth edema, tongue edema, swollen tongue, mouth swelling, angioedema, respiratory tract edema, chills, hypoxia, pruritis, rash macular, rash maculo-papular, rash erythematous, rash, and respiratory distress. The analysis was restricted to events which occurred the day of the infusion of naxitamab or the day following an infusion.

Additionally, hypertension is described in the Warnings and Precautions section of product labeling. The most common adverse reactions (≥25%) to naxitamab were infusion-related reaction, pain, tachycardia, vomiting, cough, nausea, diarrhea, decreased appetite, hypertension, fatigue, erythema multiforme, peripheral neuropathy, urticaria, pyrexia, headache, injection site reaction, edema, anxiety, localized edema and irritability. The most common Grade 3 or 4 laboratory abnormalities (≥5% in either study) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased platelet count, decreased potassium, increased alanine aminotransferase, decreased glucose, decreased calcium, decreased albumin, decreased sodium and decreased phosphate.

{DANYELZA, naxitamab-gqgk}

Clinically relevant adverse reactions in $\leq 10\%$ of patients who received naxitamab with GM-CSF in either study included apnea, hypopnea, generalized edema, peripheral edema, device related infection, anxiety, unresponsiveness to stimuli, and somnolence. Events of apnea, hypopnea, unresponsiveness and somnolence may be related to concomitant administration of opioids or to co-occurring events of severe infusion reactions, such as severe hypotension.

The safety population included patients 1 to 24 years of age across both studies, with a median age of 5 years in both studies. Although relatively few young adult patients and very young patients (2 years of age or younger) were enrolled, exploratory analyses of safety trends did not demonstrate a significant difference in safety across groups.

Overall benefit:risk assessment: Given the rarity of relapsed or refractory high-risk neuroblastoma and the lack of an approved or standard treatment, a randomized trial of naxitamab is not likely to be feasible in this population. The review team considers that the ORR in the two trials, along with the observed duration of responses, in patients treated with naxitamab is sufficient to establish clinical benefit in the rare group of patients with high risk neuroblastoma. Data from additional patients in this patient population including ORR and duration of response, may be required to confirm clinical benefit. The risks associated with naxitamab appear acceptable in the setting of patients with relapsed or refractory neuroblastoma who have no approved therapies. Naxitamab is expected to be administered in infusion centers with intensive monitoring and the ability to quickly respond to events such as severe infusion reactions. In addition, the existence of previously approved products in the US (dinutuximab) with a similar mechanism of action and toxicity profile means that the majority of pediatric oncologists administering naxitamab will have familiarity with expected toxicities associated with anti-GD2 antibodies. The review team considered the available safety and pharmacokinetic data, as well as the unmet medical need across age groups, in determining the age range (pediatric patients 1 year and older, as well as adult patients) included in the indication statement.

In the opinion of the review team, naxitamab, in combination with GM-CSF, has a favorable benefit-risk profile for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Neuroblastoma is the most common extracranial tumor in children, with approximately 800 cases diagnosed each year in the United States (American Cancer Society website, 2020). • More than 50% of these patients present with distant metastasis (Stage 4, high-risk neuroblastoma) at the time of diagnosis, typically in the bone and bone marrow (Matthay, 1997). • Ten to 50% of patients with high-risk neuroblastoma do not achieve a remission after induction/consolidation therapy and are classified as refractory; 50% to 60% of those who complete the treatment will relapse (Cole, 2012; Marris, 2007; Cotterill, 2000). • The two-year post-progression/relapse survival rates range from 8% to 29%, and 10-year overall survival (OS) rates are approximately 14% (Cotterill, 2000).	Relapsed or refractory high-risk neuroblastoma in the bone or bone marrow is a serious and life threatening disease with a high unmet medical need.
Current Treatment Options	• There are no FDA approved treatments for relapsed or refractory neuroblastoma with bone or bone marrow involvement (PDQ, 2020). • Patients are encouraged to enroll on clinical trials, are treated with off-label treatment or with palliative care. • Off label treatments include the following options (these data has not been reviewed by FDA): – Chemotherapy with immunotherapy (temozolomide/irinotecan/dinutuximab); reported ORR 53% in a 25 patient	All currently available treatment options are palliative and are associated with significant toxicity. Safe and effective treatments for this highly morbid condition are needed.

{DANYELZA, naxitamab-gqgk}

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	study. – 131I-MIBG alone or in combination with stem cell rescue; reported response rates of 20-40% – ALK inhibitors for patients with ALK mutations; reported response rate of 20%. – chemotherapy (topotecan with cyclophosphamide or etoposide; temozolomide with irinotecan; reported ORR 15-50%.	
<u>Benefit</u>	• Substantial evidence of effectiveness of naxitamab in combination with GM-CSF for the treatment of patients with relapsed or refractory high-risk neuroblastoma with bone or bone marrow involvement was based on data from 22 patients in Trial 201 and 38 patients in Trial-230 who had achieved at least stable disease, minor response, or partial response to prior treatment and received at least one dose of naxitamab in combination with GM-CSF. • The confirmed overall response rate (ORR) in Trial 201 per blinded independent review was 45% (95% CI: 24%, 68%), with 30% of the 10 responders having observed DOR of at least 6 months. • The confirmed ORR in Trial 12-230 per blinded independent review was 34% (95% CI: 20%, 51%), with 23% of the 13 responders having observed DOR of 6 months.	Substantial evidence of effectiveness was demonstrated for naxitamab in the patient population being indicated. In order to verify and further characterize the benefit for this population across multiple centers and to provide a more precise estimate of ORR, a post-marketing requirement (PMR) will be issued to collect data on a minimum of 80 patients from a minimum of six sites with at least 5 patients enrolled per site in at least 5 sites. Patients with a response will be followed for at least 12 months from the onset of response or until disease progression,

{DANYELZA, naxitamab-gqgk}

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In vitro data demonstrating ADCC with mu3F8 (a previously studied, murine form of naxitamab) was provided to support the contribution of effect of GM-CSF. Dose-dependent ADCC was demonstrated with m3F8, while adding GM-CSF resulted in a reduction in concentration of mu3F8 required to mediate ADCC.	whichever comes first.
Risk and Risk Management	• The safety of naxitamab in combination with GM-CSF was evaluated in a subpopulation of patients from Trial 201 (n=25) and 12-230 (n=72) who received the recommended phase 2 dose of naxitamab (3 mg/kg/day) intravenously on Days 1, 3, and 5 of each cycle and GM-CSF 250 µg/m²/day subcutaneously on Days -4 to 0 and GM-CSF 500 µg/m²/d subcutaneously on Days 1 to 5. • No deaths related to naxitamab were reported for either trial. • Naxitamab can cause serious infusion-related reactions and neurologic toxicity, including severe pain, transverse myelitis and reversible posterior encephalopathy syndrome (RPLS). Given the potential severity of these adverse reactions and the occurrence of infusion related reactions and pain in most patients in either trial, a boxed warning was included in the product label. Hypertension is included in the Warnings and Precautions of the product label. The most common adverse reactions (≥25% in either study) were infusion-related reaction, pain, tachycardia, vomiting, cough, nausea,	The safety profile of naxitamab is acceptable in the context of the seriousness of refractory or relapsed high-risk neuroblastoma and the risk can be appropriately mitigated through product labeling for Danyelza. This regimen will be administered by highly trained health care providers and physicians in tertiary care centers specialized for the treatment of patients with cancer. In order to fully characterize the risk of infusion-related toxicity, a PMR will be issued to conduct a comprehensive analysis evaluating and characterizing the incidence, clinical presentation, management and outcome of the potential serious risk of naxitamab-associated infusion-related reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	diarrhea, decreased appetite, hypertension, fatigue, erythema multiforme,, peripheral neuropathy, urticaria, pyrexia, headache, injection site reaction, edema, anxiety, localized edema and irritability. The most common Grade 3 or 4 laboratory abnormalities ($\geq 5\%$ in either study) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased platelet count, decreased potassium, increased alanine aminotransferase, decreased glucose, decreased calcium, decreased albumin, decreased sodium and decreased phosphate.	There were no significant safety concerns identified during the review of the application requiring risk management warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

{DANYELZA, naxitamab-gqgk}

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 8.2 describes events of pain. Pain scores were collected per standard medical practice and did not include additional clinical outcome assessments.
	☐	Clinical outcome assessment (COA) data, such as	
	☐	Patient reported outcome (PRO)	
	☐	Observer reported outcome (ObsRO)	
	☐	Clinician reported outcome (ClinRO)	
	☐	Performance outcome (PerfO)	
	☐	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	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761171}

{DANYELZA, naxitamab-gqgk}

☐	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

Amy Barone, MD

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Neuroblastoma is a rare, almost exclusively pediatric cancer. Neuroblastoma is the most common extracranial tumor in children, with about 800 cases diagnosed each year in the United States[1] The majority of patients are diagnosed before the age of 2 years (60%), and almost all are diagnosed before the age of 10 years (97%).[2] More than 50% of these patients present with distant metastasis (Stage 4) at the time of diagnosis, typically in the bone and bone marrow.[3-5]

Clinical course and patient outcome are linked to the patient's risk categorization at the time of diagnosis. Risk classification is by the International Neuroblastoma Risk Group (INRG) Classification System.[6] Patients diagnosed with low-risk neuroblastoma (Stages 1, 2, and 4S, per the International Neuroblastoma Response Criteria [INRC]) or intermediate-risk neuroblastoma (Stage 3) have high survival rates, exceeding 95%. However, less than 50% of patients with high-risk disease achieve long-term survival.[6]

Among patients with high-risk neuroblastoma, 10% to 50% do not achieve a remission after induction/consolidation therapy and are classified as refractory[3, 4, 7-9] and 50% to 60% of those who complete the treatment will relapse.[3, 4]

For patients with high-risk neuroblastoma who relapse after induction/consolidation therapy, the sites of relapse are most commonly bone and bone marrow (BM). BM invasion is associated with a poor prognosis.[5, 10] The time to disease progression is another important predictor of outcome; in a follow-up analysis of relapsed patients, London et al. reported that patients at the highest risk of death were those who relapsed between 6 and 18 months after initial diagnosis (peak, approximately 12 months).[11]

No standard of care currently exists for the treatment of patients with refractory or relapsed neuroblastoma, and the outcomes have been disappointingly poor for decades; the two-year post-progression/relapse survival rates range from 8% to 29%, and 10-year overall survival (OS) rates are around 14%.[5, 12]

{DANYELZA, naxitamab-gqgk}

Hence, there is a large, unmet medical need for more effective treatments for patients with refractory or relapsed neuroblastoma with disease in bone and/or bone marrow.

The FDA's Assessment:

FDA agrees with the description provided by the Applicant.

{DANYELZA, naxitamab-gqgk}

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Standard induction therapies for high-risk neuroblastoma include surgery and five to six cycles of induction chemotherapy with agents such as cisplatin, cyclophosphamide, doxorubicin, etoposide, topotecan, or vincristine. Consolidation therapy includes myeloablative chemotherapy regimens (e.g., carboplatin-etoposide-melphalan, busulfan melphalan, or thiotepa-cyclophosphamide) with stem cell transplantation (SCT) and external-beam radiotherapy. Postconsolidation therapy to treat minimal residual disease (MRD) includes immunotherapy (e.g., dinutuximab) and cytokines (GM-CSF, interleukin-2), plus isotretinoin.[6, 13]

A patient who does not respond fully to induction therapy or who relapses during or after consolidation/postconsolidation therapy can receive salvage treatment. Widely used salvage chemotherapy regimens combine topoisomerase I inhibitors (e.g., topotecan or irinotecan) with either alkylators (e.g., cyclophosphamide or temozolomide) or topoisomerase II inhibitors (e.g., doxorubicin or etoposide). If the topoisomerase I inhibitor-based regimens are ineffective, other chemotherapy salvage regimens available include ifosfamide, carboplatin, and etoposide. Patients with refractory or relapsed neuroblastoma have poor prognoses after incomplete response to or relapse after frontline therapy, respectively.[3] Particularly, there is an unmet medical need for effective treatment of refractory and relapsed patients with disease in bone and/or bone marrow after chemotherapy, who have a high probability of developing progressive disease with no approved treatment options.

Because there are no approved treatment options for these patients, clinical trials are ongoing with investigational therapies for the treatment of relapsed or refractory neuroblastoma. Investigational therapies include CAR T-cell therapy, vaccines, antibody therapies (including anti-GD2 antibodies and checkpoint inhibitors), tyrosine kinase inhibitors, histone deacetylase inhibitors, and ornithine decarboxylase inhibitors.

Hence, the treatment of relapsed and refractory neuroblastoma remains an area of unmet medical need.

The FDA's Assessment:

FDA agrees that there are no approved therapeutic options for patients with high-risk neuroblastoma that is relapsed or refractory. Treatment options commonly used at the time of recurrence (which are not approved for this indication) may include chemotherapy as described above, ¹³¹I-MIBG alone or in combination with other therapy, or chemotherapy in combination with anti-GD2 therapies (PDQ Pediatric Treatment Editorial Board, 2020) .

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Naxitamab is not currently registered (or approved) in the United States or in any other part of the world.

The FDA's Assessment:

FDA agrees with the Applicant and has no further comment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Y-mAbs submitted IND 132793 on 05 September 2017 after acquiring the rights to naxitamab from Memorial Sloan Kettering Cancer Center (MSK). MSK had studied naxitamab under IND 112594 since 2012 and under IND (b) (4). As part of the pre-BLA meeting, FDA agreed with the use of MSK Trial 12-230 as the pivotal efficacy trial, with supportive efficacy data coming from Y-mAbs Trial 201 and retrospective Study 2PR01. MSK Trials 11-009 and 12-116 provide supportive safety data.

After interactions with FDA, key changes to the naxitamab program included, but were not limited to: (1) incorporation of independent radiology and pathology reviews into response assessments for Trial 12-230 and Trial 201, (2) completion of comparability studies between the MSK-produced naxitamab and the Y-mAbs-produced naxitamab, (3) qualification of the nude rat model as a relevant animal model for naxitamab toxicology studies, (4) inclusion of multiple potency assays in the drug product release specifications, (5) pooling of data from Trial 11-009, Trial 12-116, Trial 12-230, and Trial 201 in a population PK study, and (6) conduct of a retrospective review of the naxitamab compassionate-use program in Spain for additional efficacy and safety data.

The key regulatory history for naxitamab under IND 132793 is summarized below.

Table 3-1. Key Regulatory History - IND 132793

Regulatory Meeting	Date	Purpose of Meeting
Pre-IND Meeting	31 Jan 2017	Discuss adequacy of the existing clinical and nonclinical data to support Y-mAbs' planned clinical trial.
Type C CMC Meeting	24 Apr 2018	To reach agreement on the sufficiency of the CMC development plans for the naxitamab drug substance and drug product in preparation for submission of a BLA and subsequent commercialization.
Type C Nonclinical Meeting Written Responses	23 Sep 2018	Discuss the nonclinical program to support a BLA for refractory or relapsed neuroblastoma.
Type B CMC Meeting	06 Nov 2018	To reach agreement on the comparability study of the MSK naxitamab product and the Y-mAbs naxitamab product, omission of an assay, and the proposed process qualification and validation for the naxitamab drug substance and drug product processes in preparation for the submission of a BLA and subsequent commercialization.
Type B Multidisciplinary Meeting	06 Nov 2018	To reach agreement on the adequacy of Y-mAbs' method for response evaluation, immunogenicity, and pharmacokinetics (PK); and plans for accelerated approval.
Type B CMC Meeting Written Responses	10 Jan 2019	To reach agreement on manufacturing activities that must be completed relative to a BLA submission.
Type B Pre-BLA Meeting	26 Jun 2019	To reach agreement on the content of the BLA, immunogenicity, and the timing for a rolling submission and planned safety update.
Type B CMC Pre-BLA Meeting Preliminary Comments	06 Sep 2019	Discuss the format, content, and submission schedule for the CMC module of the naxitamab BLA.

The FDA's Assessment:

The above summary captures the intent of meetings under IND 132793. FDA notes that the initial clinical trials with naxitamab were conducted under IND 112594, held by Memorial Sloan Kettering Cancer Center (MSKCC). Trial 12-230, a primary study supporting efficacy and safety for the BLA, was conducted under the MSKCC IND.

FDA placed IND 132793 on partial clinical hold on October 3, 2017 due to CMC issues; specifically, there was insufficient information to assess risks to human subjects. Y-mAbs was permitted to use only a single lot in their Study 201 trial and no other lots could be used until Y-mAbs proposed a strategy to improve the performance of the ADCC-CD16, ADCC-CD32, and

{DANYELZA, naxitamab-gqgk}

CDC assays and establish a meaningful acceptance criterion for each assay. The partial hold was removed on June 7, 2018 after Y-mAbs provided a complete response to partial clinical hold addressing these deficiencies.

Agreements at the November 6, 2018 Type B meeting are summarized below:

- FDA agreed that Y-mAbs's justification for the GM-CSF dosing regimen in combination with naxitamab in patients aged 12 months and older who have relapsed or refractory neuroblastoma high-risk neuroblastoma is acceptable and stated that a final determination of the adequacy of the dosing regimen will be made at the time of review of the planned BLA submission.
- FDA stated that in the context of a single-arm, single center study, a blinded independent review of all imaging and pathologic response data by expert pediatric radiologists and pathologists outside of MSKCC will reduce the risk for reader bias and be the most reliable process for the efficacy determination.
- FDA agreed that demonstration of an effect on centrally reviewed ORR of sufficient magnitude and duration with an acceptable safety profile for naxitamab in the intended patient population might support the accelerated approval of naxitamab, in combination with GM-CSF, for the treatment of high-risk neuroblastoma refractory to initial therapy or with incomplete response to salvage therapy in patients >12 months of age with (b) (4), refractory disease in bone marrow, (b) (4) or bone (b) (4). FDA stated that the final indication will depend on review of the efficacy data for all patients and relevant subgroups.
- FDA stated that a well-defined patient population with regard to extent of disease and prior therapy, including localized treatments (e.g., patient is not a candidate for radiation or surgical resection), is necessary for an overall benefit: risk assessment of naxitamab in the subgroup of patients with disease isolated to bone.
- FDA agreed that the proposed ORR, DOR and safety analyses from Study 12-230, depending on the results, could be submitted in a BLA. FDA requested that any early efficacy data from the expanded access trial or Y-mAbs Study 201 also be submitted in the BLA, given that Study 12-230 is limited to a single institution's experience, and given that the product administered to patients in the trials was different.
- FDA stated that the proposed efficacy endpoint of PFS rate at 2 years will be considered exploratory. To make an attempt at an assessment of the effect of naxitamab on PFS as compared to a historical data analysis, eligibility criteria with regard to disease-related prognostic factors and prior therapy should be the same as historical controls based on

{DANYELZA, naxitamab-gqgk}

all relevant literature. [REDACTED] (b) (4)

- FDA stated that the full analysis set should include all patients from both parts of Study 12-230 who were treated at or above the recommended dose and who have [REDACTED] (b) (4) disease that would fall under the proposed indication for accelerated approval.
- With regard to use of Study 201 as a confirmatory trial, FDA acknowledged the challenges inherent in designing a randomized trial of naxitamab to serve as the confirmation of clinical benefit in the population of interest. FDA advised that Y-mAbs still include in the BLA a clear and thoughtful justification for not conducting an internally controlled trial to characterize naxitamab's effect on a survival endpoint. Additionally, FDA made the following recommendations for Study 201: 1) All patients should be followed for a minimum of 12 months after the onset of response from the last responding patient to better characterize the durability of response, and 2) OS should be incorporated as a key secondary endpoint to assess for possible impairment in OS as compared to historical data and to further characterize safety. FDA recommended that patients be followed for survival for at least two to five years.
- FDA strongly recommended that Y-mAbs verify all the data from all patients enrolled in Study 12-230 prior to submitting datasets in an application and that Y-mAbs also verify that the study information submitted in the application is correct (e.g., pertaining to investigators and conflict of interest).

Agreements at the June 26, 2019 pre-BLA meeting are summarized below:

- FDA generally agreed that the results from Studies 12-230 and 201 will provide the primary support for the BLA and that results from Studies 11-009, 12-116 and 2PR01 will provide supportive safety information. FDA provided guidance regarding the content of the safety narratives.
- FDA advised that In addition to the primary efficacy analysis that will include patients in Study 12-230 with evaluable disease at baseline who were treated at the intended recommended dose level (9.0 mg/kg per cycle), Y-mAbs include exploratory response rate analyses for the groups of patients with evaluable disease at baseline who were 1) treated at doses lower than 9.0 mg/kg/cycle, and 2) who were treated with any dose of naxitamab. FDA also strongly recommended that Y-mAbs conduct an independent review of the available Study 201 response data planned for inclusion in the BLA. Depending on the timeline for submission of the BLA, Y-mAbs should also update the Study 201 efficacy data

{DANYELZA, naxitamab-gqgk}

cut-off dates to allow for an increased number of patients in this important supportive efficacy analysis. FDA advised that in the event that naxitamab received FDA approval, the final indication would depend on review of the efficacy data for all patients and relevant subgroups.

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

4.1. Office of Scientific Investigations (OSI)

One clinical site, Memorial Sloan Kettering Cancer Center (MSKCC) was selected for inspections because all patients enrolled in Trial 12-230 and 8 of 25 patients enrolled in the safety population of Trial 201 were treated at this site. The only other site at which more than one patient in the efficacy population for Trial 201 was treated was Hospital Sant Joan de Deu, located in Spain, which enrolled 16 of 25 patients in the safety population. Given the challenges associated with international travel during the COVID-19 pandemic and the ability to inspect the MSKCC site (Principal Investigator Dr. Brian Kushner) which generated the majority of the clinical data across studies, inspection of the clinical site in Spain was not deemed critical to the application review.

Review of inspections of the imaging facility used for independent central assessment of ORR and DOR, (b) (4), were last completed in July 2018 and had been inspected three times since 2012. Each inspection had a compliance classification of No Action Indicated. Therefore, inspection of the imaging facility was not deemed necessary for this application.

The inspection of the MSKCC clinical site conducted by the Office of Scientific Investigations revealed no significant findings. The studies appear to have been conducted adequately and there was no evidence of underreporting of serious adverse events or significant protocol deviations. Based on the inspection, the data generated by the inspected clinical investigator appear to be acceptable in support of the BLA.

4.2 Product Quality

The Office of Pharmaceutical Quality recommended approval of this BLA.

The following is reproduced from the OPQ Executive Summary dated October 7^t, 2020.

Recommendation: BLA Approval

Primary Reviewer Summary Recommendation:

In totality, the information in this Biologics License Application (BLA) (STN 761171) support the conclusion that the manufacture of Danyelza (naxitamab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious agents and meets the standards recommended by the FDA. The conditions used in the commercial manufacturing process are supported by sufficient validation data, with additional data committed by the Sponsor as part of a pre-BLA agreement. The product has been consistently produced from multiple production runs. It is recommended that Danyelza (naxitamab) be approved for human use under the conditions specified in the package insert.

4.3. Clinical Microbiology

The Clinical Microbiology review team recommended approval of this BLA.

The following is reproduced from the September 30th, 2020 review from the Office of Biotechnology Products (OBP)

Primary Reviewer Summary Recommendation:

The final recommendation for approvability is pending the submission of the completed DS PPQ4 submission material. An addendum will be filed to this review with the final recommendation.

4.4. Devices and Companion Diagnostic Issues

Not applicable. A companion diagnostic test was not submitted with the Application, and a companion diagnostic is not necessary for the safe and effective use of naxitamab for the recommended indication.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment:

Naxitamab (hu3F8-IgG1) is a humanized monoclonal antibody against the ganglioside GD2, which is a member of the b-series gangliosides and an adhesion molecule widely expressed on the cell membrane in neuroectoderm-derived tumors; the established pharmacological class is GD2-binding monoclonal antibody.. An earlier version of the antibody studied clinically, a mouse anti-GD2 monoclonal antibody coded m3F8, had promising clinical outcomes in patients with neuroblastoma; however, m3F8 also had significant immunogenicity in patients, leading the original investigators to develop the humanized version of m3F8, naxitamab. Naxitamab has the same epitope-targeting region of the murine antibody. In binding studies, naxitamab bound to human GD2 with a K_D of 19.8 nM. Naxitamab had no off-target binding to other gangliosides including GM2, GD1a, GT1b, GD3, and GQ1b, and had minimal binding to ganglioside GD1b (4.5% compared to maximal binding to GD2).

In the absence of human serum or effector cells, naxitamab had direct cytotoxicity against the GD2 expressing human neuroblastoma cell line LAN-1 with EC_{50} values of 5 μ g/mL (approximately 29 times lower than the C_{max} of 147 μ g/mL in patients treated with naxitamab for multiple cycles on Days 1, 3, and 5 at 9.0 mg/kg). In antibody dependent cellular cytotoxicity (ADCC) assays, including assays using human peripheral blood mononuclear cells (PBMCs), polymorphonuclear leukocytes (PMNs), or CD16 or CD32 expressing NK cell lines as effector cells, naxitamab showed significantly increased activity against high GD2-expressing LAN-1 neuroblastoma target cells and 5 other GD2-expressing cell lines compared to the original murine version of the antibody. Conversely, naxitamab had mild decreases in CDC-mediated cytotoxicity compared to the murine parent antibody. No tested anti-GD2 antibody mediated significant ADCC or CDC activity against a low GD2-expressing cell line. Investigators also showed that the addition of granulocyte-macrophage colony stimulating factor (GM-CSF) to PBMC cultures resulted in concentration-dependent increases in m3F8-mediated ADCC against human neuroblastoma cell lines of up to 30% compared to m3F8 alone, providing support for the use of GM-CSF in the clinical dosing regimen for naxitamab.

In an in vivo study, twice-weekly IV naxitamab administration resulted in dose-dependent anti-tumor activity in mice bearing LAN-1 subcutaneous tumors and decreased tumor size to a greater extent than m3F8 given on the same schedule. Further, Bergman and colleagues (1993) showed that m3F8 alleviated paraparesis caused by epidurally-implanted metastatic

{DANYELZA, naxitamab-gqgk}

neuroblastoma in a rat model due to m3F8-induced shrinkage of tumors in the epidural space. The Applicant submitted additional in vivo data from publications using a surrogate anti-GD2 antibody targeting a separate GD2 epitope to further explore the known naxitamab-related clinical side effect of pain. Intravenous or intrathecal administration of a murine IgG2a isotype anti-GD2 monoclonal antibody (14.G2a) to adult immunocompetent Sprague Dawley rats led to mechanical allodynia, confirming the enhanced pain effect of anti-GD2 administration in animals.

The initial clinical trials investigating the activity and dosing of naxitamab were conducted on the basis of previous clinical data with the murine parent antibody rather than supported by toxicology data with the clinical candidate. As clinical development proceeded, FDA advised the manufacturer that the Agency would expect additional animal toxicology data to support a future BLA submission. The investigators asserted that nude rats rather than a non-human primate would be a reasonable toxicology model and confirmed the presence of NK cells and PMN in these animals prior to conducting toxicology studies. Investigators reasoned that the use of nude rats rather than fully immune competent animals would allow for avoidance of the formation of anti-drug antibodies that would prevent long-term assessment of a human antibody in a rodent model. To help address FDA concerns regarding the use of immunodeficient rats as pharmacologically relevant species for toxicological testing of naxitamab, Y-mAbs also evaluated the ability of naxitamab to mediate ADCC using effector cells from nude rats against rat GD2-expressing target cells and compared these effects to naxitamab-induced ADCC using human effector cells against human GD2-expressing target cells. Naxitamab did bind to both rat GD2 and to splenocytes from nude rats; however, in the presence of nude rat splenocyte effector cells, naxitamab did not induce ADCC against GD2-expressing rat PC12 cells and induced only ~10% cytotoxicity in GD2-expressing rat C6 cells. Naxitamab induced approximately 22% ADCC in human LAN-1/rat splenocyte co-cultures whereas there was 55% ADCC against the same cell line in the presence of human NK cells, indicating that the rat/rat and rat/human systems underpredicted the activity of the human/human system. Naxitamab also led to 24 to 54% ADCC at 30 and 100 µg/mL, respectively, against another GD2-expressing human neuroblastoma cell line, IMR-32. Additional studies to support selection of the nude rat for use in pivotal toxicity studies included evaluation of the reactivity of naxitamab in tissue cross-reactivity studies using peripheral nerve, skin, spinal cord, and brain sections from human, Sprague-Dawley rat, and nude rats. Staining with naxitamab occurred in the cerebral cortex, cerebellum, spinal cord, and peripheral nerve in tissues, and skin from human and both rat strains. Significantly stronger positive staining occurred in human tissues compared to both rat strains.

{DANYELZA, naxitamab-gqgk}

Y-mAbs conducted a GLP-compliant 13-week toxicology study in nude rats. Rats received intravenous naxitamab for 4 cycles of 3 treatment days per cycle (every other day on Days 1, 3, and 5) at doses of 0, 10, or 50 mg/kg. Exposures achieved in rats at the 50 mg/kg dose level were 32 (males) and 25 (females) times higher than the AUC in patients (2386 $\mu\text{g}\cdot\text{h}/\text{mL}$) at the once every 3 days per cycle clinical dose of 9 mg/kg. Multiple deaths occurred in all dosing groups including the control group, with mortality rates of 13% in controls, 20% in the 10 mg/kg group, and 13% in the 50 mg/kg group; the causes of death were undetermined and without notable patterns of clinical signs or pathology, suggesting that they were not related to the test-article. In surviving animals, naxitamab-related toxicity was generally mild. Naxitamab caused decreased body weight gain of up to 12% in both the 10 and 50 mg/kg groups compared to control animals which persisted into the recovery phase. Rats treated with both doses of naxitamab showed minimal increases in reticulocytes, neutrophils, lymphocytes, eosinophils, basophils, platelets, and APTT with no dependence on dose level, and decreased prothrombin in the 50 mg/kg group as well as minimal increases in urea and potassium. All clinical chemistry and hematology findings recovered by the end of the recovery period. Minor decreases in organ weights of the thyroid/parathyroid occurred at both dose levels. Gross pathology findings were limited to the stomach with depression and thickening noted at both dose levels which was further supported by histopathology findings of hyperplasia, inflammation, and erosion of the stomach. Additional histopathology findings included minimal to moderate inflammatory cell infiltrate/inflammation of the plantar and tibial nerves in treated males. Evaluation of nociception (pain response) using an analgesiometer and application of increasing pressure on the paw between a flat surface and a blunt pointer showed a mild increase in pain threshold, which is in contrast to the expected pharmacological response due to treatment with an anti-GD2 antibody, and in contrast to the responses shown by Sprague Dawley rats treated with a surrogate anti-GD2 antibody as reviewed in the pharmacology section as well as clinical findings of increased pain sensitivity. The lack of increased pain response in adult nude rats and a similar lack of a clear effect in a non-GLP dose range finding study in juvenile nude rats coupled with the in vitro ADCC data using nude rat effector and target cells showing significantly reduced activity compared to the human counterparts suggests that the immunodeficient nude rat does not fully recapitulate the activity of drug and therefore does not appear to be a reasonable strain for assessing the toxicological effects of naxitamab.

Y-mAbs did not conduct dedicated studies to assess fertility or carcinogenicity and these studies are not warranted to support the development of a drug intended to treat patients with advanced cancer. In addition, because the age of the proposed patient population is primarily ≤ 5 years old, FDA did not request an embryo-fetal development study to support the use of naxitamab. As IgG1 antibodies can cross the placenta with increasing frequency as pregnancy persists and because naxitamab can bind to normal GD2 expressing cells of neuroectodermal

{DANYELZA, naxitamab-gqgk}

origin, including the central nervous system and peripheral nerves, a warning for embryo-fetal toxicity is included in the label.

Given the concerns regarding the model used for the toxicological assessment (nude rats), the nonclinical team cannot conclude that the toxicity of naxitamab has been adequately tested in animal models to look for any consequences related chronic administration of this product. Given the unusual development history, the application appears approvable based on the strength of the available clinical data in the proposed patient population with few clinical options; however, the nonclinical team will request a post-marketing requirement (PMR) to further explore the toxicity of naxitamab given for a minimum of 2 cycles in a relevant animal species. Because of the age of the intended patient population and the lack of significant clinical experience in adult patients and the focus on potential effects on nerve development, this PMR study should be conducted in juvenile animals.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for naxitamab.

The FDA's Assessment:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for naxitamab.

5.3. Pharmacology

Primary pharmacology (all data entered by FDA)

A. In Vitro Studies

Binding

In Study #YMAB_GD2_AFFI_BIAC_ARP_02, naxitamab (hu3F8-IgG1) bound to human GD2 with greater affinity than either of the 14.18-based anti-GD2 antibodies, dinutuximab beta or Unituxin (K_{Ds} of 19.8 nM vs. 251 and 169 nM, respectively) as measured via surface plasmon resonance (SPR). In addition, the Applicant cited data from Cheung et al. 2012, showing that compared to alternate anti-GD2 antibodies 14.G2a and ME36.1, both humanized (hu3F8-IgG1 [naxitamab] and hu3F8-IgG4) and chimeric 3F8 antibodies had higher affinity for human GD2 as

{DANYELZA, naxitamab-gqgk}

measured by SPR (Table 2). Naxitamab binding affinity for GD2 was similar to the affinity of the murine parent antibody, m3F8.

Table 5-1: Binding affinity of humanized and chimeric anti-GD2 antibodies for human GD2

Antibody	K _D (nM)	Antibody	K _D (nM)
hu3F8-IgG1	11	m3F8	5
hu3F8-IgG4	15	14.G2a	77
ch3F8-IgG1	13	ME36.1	19
ch3F8-IgG4	14	-	-

Hu – humanized antibodies. Ch – chimeric antibodies. m3F8 is a murine IgG3 anti-GD2 antibody. 14.G2a is derived from the clinically tested 14.18 anti-GD2 antibody (Cheung et al. 2012).

Finally, naxitamab did not bind to gangliosides GM2, CD1a, GT1b, GD3, or GQ1b though there was minimal binding to GD1b (approximately 4.5% relative to GD2) as measured via ELISA (Cheung et al. 2012).

Antibody-mediated toxicity

Cheung et al. (2012) showed that in the absence of human serum or human effector cells naxitamab had cytotoxic activity against the GD2-expressing human neuroblastoma cell line, LAN-1, with an EC₅₀ of 5 µg/mL, comparable or more potent compared to the previous clinical candidate m3F8 and a murine IgG2a isotype variant of another clinically studies anti-GD2 targeted antibody, 14.G2a (2 and 47 µg/mL, respectively). In addition, using a chromium release assay investigators compared naxitamab-induced antibody-dependent cellular cytotoxicity (ADCC) relative to parent antibody m3F8-induced ADCC using human peripheral blood mononuclear cells (PBMCs) in the presence of IL-2 or human polymorphonuclear leukocytes (PMN) as effector cells and LAN-1 cells as target cells at a 50:1 ratio in the presence of GM-CSF. Similar assays were conducted using IL-2 independent natural killer (NK-92MI) cells expressing human CD16 or CD32 Fc receptors at a ratio of 20:1 and without the addition of cytokines. In addition, the authors assessed GD2-directed antibody-mediated complement dependent cytotoxicity (CDC) compared to the murine parent antibody for naxitamab (m3F8). Relative to m3F8, naxitamab (hu3F8-IgG1) showed significant increases ADCC activity against the LAN-1 neuroblastoma cell in line in the PBMC and PMN assays as well as all other assays assessing ADCC (Table 3). Conversely, naxitamab had decreased CDC activity compared to the murine parent. The IgG4 isotype of hu3F8 did not have appreciable activity in any assay conducted (data not shown).

{DANYELZA, naxitamab-gqgk}

Table 5-2: ADCC and CDC activity of naxitamab compared to m3F8 and 14.G2a

Antibody	PBMC	PMN	NK-92MI-CD16	NK-92MI-CD32	CDC
ch3F8-IgG1	390	18	24	13	0.64
hu3F8-IgG1	217	19	12	15	0.40
m3F8	1	1	1	1	1
14.G2a	0.03	1	4	2	0.12

All values are represented relative to m3F8; Hu – humanized antibodies. Ch – chimeric antibodies (EC_{50} m3F8/ EC_{50} for antibody listed; Cheung et al. 2012).

There were similar ADCC and CDC results in seven different GD2-expressing neuroblastoma cell lines, but not in the SKNJC2 neuroblastoma line, which had much lower GD2 expression.

Table 5-3: ADCC and CDC activity against neuroblastoma cell lines

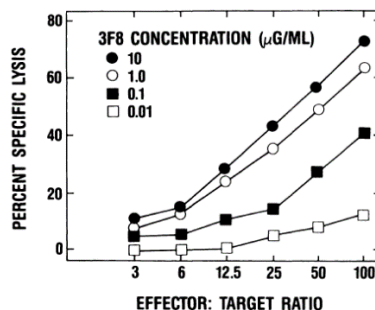
Antibody	LAN1	NMB7	SKNLP	BE(1)N	SKNMM	SKNAS	SKNJC2
ADCC-NK92-CD16							
Naxitamab	14	31	12	36	29	31	-
14.G2a	2	1	1	1	0.1	-	-
ADCC-NK92-CD32							
Naxitamab	15	7	1469	62	58	13	-
14.G2a	2	2	70	4	1	0.3	-
CDC							
Naxitamab	0.4	0.27	0.59	0.2	0.22	0.11	-
14.G2a	0.46	0.05	0.1	0.01	0.01	0.02	-

All values are represented relative to m3F8 (EC_{50} m3F8/ EC_{50} for antibody listed; Cheung et al. 2012).

Kushner and Cheung (1989) showed that incubation with m3F8 led to concentration-dependent increases in ADCC against the neuroblastoma cell line NMB7 in the presence of effector granulocytes (~97% neutrophils (PMNs)) at varying effector to target cell ratios (E:T range of 0.01:1 to 10:1), with an EC_{50} value of 0.1 μ g/mL (Figure 1); the addition of GM-CSF enhanced this effect (Table 5). In the presence of effector PMNs, m3F8 was able to mediate ADCC against GD2-expressing but not GD2-negative target cells in (Table 6).

{DANYELZA, naxitamab-gqgk}

Figure 1: m3F8-mediated ADCC by PMNs against NMB7 cells



(Excerpted from Kushner and Cheung 1989)

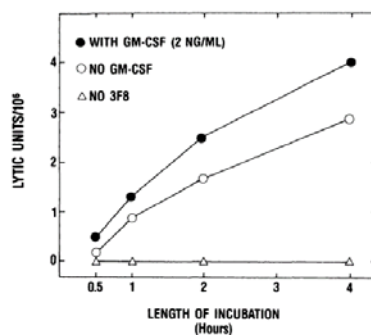
Table 5-4: GM-CSF enhancement of m3F8-mediated ADCC by PMNs against LAN-1 and NMB7 cells

GM-CSF (ng/mL)	E:T Ratio					
	LAN-1			NMB-7		
	50:1	25:1	12:1	50:1	25:1	12:1
0	34	23	16	46	37	21
0.002	36	35	19	66	43	27
0.02	50	40	22	66	49	32
0.2	53	35	25	71	56	42
2.0	61	43	25	74	57	36
20.0	67	49	29	72	60	36

(Excerpted from Kushner and Cheung 1989)

Values expressed as percent lysis. mu3F8 = 2 µg/mL.

Figure 2: Time course of GM-CSF increase in ADCC of NMB7 cells by m3F8



(Excerpted from Kushner and Cheung 1989)

{DANYELZA, naxitamab-gqgk}

Table 5-5: m3F8-mediated ADCC using PMN as effector cells

Cell Lines	No. of Experiments	E:T Ratio					
		100:1		50:1		25:1	
		3F8	No 3F8	3F8	No 3F8	3F8	No 3F8
Neuroblastoma (G ₀ ₂ positive)							
NMB-7	6	65	1	56	3	43	2
IMR-6	7	62	2	47	2	35	2
LAN-1	7	60	1	48	0	30	1
LAN-5	2	44	0	30	0	21	0
Melanoma (G ₀ ₂ positive)							
SKMel-1	14	48	2	27	1	13	2
SKMel-31	3	42	0	24	0	10	0
HT-144	6	28	0	17	0	9	1
M-14	11	25	1	16	1	9	1
Other (G ₀ ₂ negative)							
Daudi	1	0	0	0	0	0	0
K562	2	6	6	5	5	4	2
SKNMC	1	2	2	0	0	0	0
SKNSH	3	0	0	0	1	0	1

Results are expressed as percent specific target cell lysis. Data are arithmetic means. 3F8 = 10 µg/mL final concentration.

(Excerpted from Kushner and Cheung 1989)

Similarly, Munn and Cheung, 1990 showed that the m3F8 antibody was able to mediate antibody dependent cellular phagocytosis (ADCP). Investigators cultured human monocytes with CSF to enhance macrophage maturation and labeled cells with anti-CD14/CD-11b-PE antibodies then incubated these monocytes/macrophages with PKH2 (green fluorescent dye)-labelled GD2-expressing neuroblastoma cells (LAN-1) for 8 to 24 hours. The authors then measured internalization of green dye-labeled cells by microscopy or flow cytometry. In the presence of m3F8, there were high levels of target cell engulfment (data not shown). The authors did not include the clinical candidate, naxitamab, in this assessment.

Species Selection

To help justify use of the immune deficient nude rat as a relevant model for the toxicological assessment of naxitamab, in Study # NM52RT the Applicant evaluated the ability of naxitamab to mediate ADCC using effector cells from nude rats against rat GD2-expressing target cells and compared the results to naxitamab-induced ADCC using human effector cells against human GD2-expressing target cells.

Evaluation of GD2 levels in GD2-expressing rat cell lines (B35 neuronal neuroblast, C6 glial tumor, F98 glioblastoma, PC12 adrenal pheochromocytoma) via flow cytometry led investigators to choose C6 and PC12 cells as rat target cells. Based on mean fluorescent intensity, naxitamab showed higher binding to C6 and PC12 cells compared to B35 and F98 rat cells but binding intensity was significantly lower on rat cells compared to human neuroblastoma LAN-1 cells known to express GD2 (Table 7). In addition, investigators assessed binding of naxitamab to natural killer (NK) cells from nude rats (identified using an anti-rat NK cell receptor CD161 antibody) in nude rat splenocytes. Double binding of naxitamab and CD161

{DANYELZA, naxitamab-gqgk}

occurred in approximately 19% of rat splenocytes, suggesting engagement of the human Fc domain of naxitamab by some percentage of NK cells in nude rats.

Table 5-6: Naxitamab binding to rat and human target cells

Cell Line	3.1 µg/mL	12.5 µg/mL	50 µg/mL
C6	3967	3955	4070
PC12	2780	2926	3259
B35	73	238	955
F98	55	432	1471
LAN-1	475543	1130817	1781574

Values are mean fluoresce intensity. LAN-1 served as the positive control.

Investigators treated fluorescently labeled (calcein-AM) GD2-expressing target cells (C6, PC12 for nude rat; human neuroblastoma cell lines LAN-1, IMR-32 for human) co-cultured with primary human NK cells or splenocytes from nude rat as effector cells with naxitamab (0, 30, 100 µg/mL) for 4 hours at an effector:target ratio of 4.2:1 for rat cells and 8.5:1 for human cells. Triton (0.5%) served as a positive control for 100% cell death. Human LAN-1 cells incubated with rat splenocytes served as a positive control for activity of rat effector cells in the rat ADCC assays. In the presence of nude rat splenocytes naxitamab did not induce ADCC against rat PC12 cells but induced mild cytotoxicity in rat C6 cells (10% and 8% at 30 and 100 µg/mL, respectively), compared to absence of naxitamab (Table 8). Naxitamab induced approximately 22% ADCC in LAN-1/rat splenocyte co-cultures.

Table 5-7: Percent Naxitamab-Mediated Cytotoxicity by Nude Rat Splenocytes against Rat or Human Cells

Target Cells	Condition	4 hrs Percentage Cytotoxicity
PC-12 (Rat GD-2 Expressing)	PC-12+Nude Rat SC+Nax 100 µg/mL	-1
	PC-12+Nude Rat SC+Nax 30 µg/mL	3
	PC-12+Nude Rat SC	0
	PC-12 Background	N/A
	PC-12 100% Release	N/A
C6 (Rat GD-2 Expressing)	C6+Nude Rat SC+Nax 100 µg/mL	8
	C6+Nude Rat SC+Nax 30 µg/mL	10
	C6+Nude Rat SC	0
	C6 Background	N/A
	C6 100% Release	N/A
LAN-1 (Human GD-2 Expressing)	LAN-1 + Rat SC+Nax 100 µg/mL	22
	LAN-1 Background	N/A
	LAN-1 100% Release	N/A

SC=splenocytes;

(Table adapted from Study NM52RT)

{DANYELZA, naxitamab-gqgk}

Naxitamab induced ADCC at both 30 and 100 µg/mL using human NK cells and human LAN-1 or IMR-32 cells compared to no antibody control.

Figure 3: Naxitamab-induced ADCC using human LAN-1 or IMR-32 cells and human NK cells

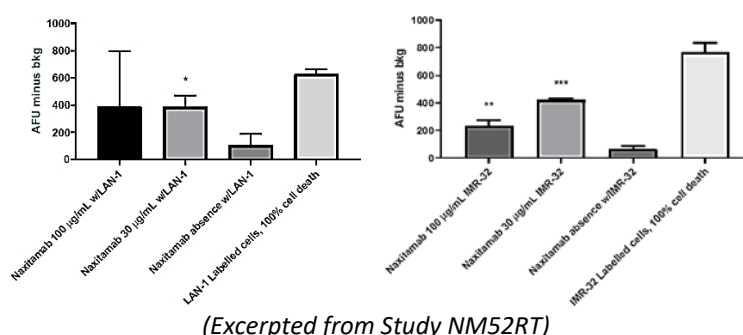


Table 5-8: Percent naxitamab-induced ADCC using human effector and target cells

Percentage Cytotoxicity	Target cell line	Naxitamab 100 µg/mL final	Naxitamab 30 µg/mL final
	LAN-1	55%*	54%
	IMR-32	24%	51%

(Excerpted from Study NM52RT)

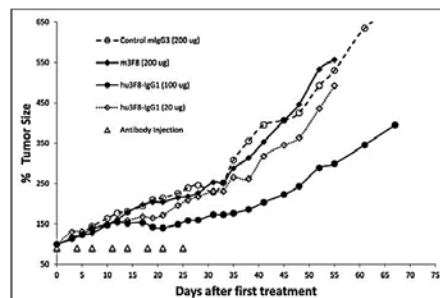
*Applicant states this data is for informational purposes only due to high SD between replicates as shown above in graph for LAN-1.

While the ADCC data does suggest that there was some ADCC activity by rat splenocytes, the activity using nude rat cells against rat targets was less robust than ADCC against human cells in the presence of human NK cells (maximum 10% for nude rat SC against rat GD-2 expressing cells vs. maximum 55% for human PBMCs against high expressing human GD-2 LAN-1 cells). This data did not provide clear support for the use of the nude rat as a species for toxicological assessment of naxitamab.

B. In Vivo Studies

Athymic mice implanted subcutaneously with LAN-1 tumors began twice weekly treatment with naxitamab at dose levels of 20 or 100 µg for a total of eight doses after tumors reached a volume of ~200 mm³. Treatment with naxitamab had minimal activity at the 20 µg dose level, with increased activity at 100 µg; m3F8 at 200µg on the same schedule had no clear effect (Cheung et al. 2012).

{DANYELZA, naxitamab-gqgk}

Figure 4: Anti-tumor activity of naxitamab and m3F8 in adult mice bearing subcutaneous LAN-1 tumors

(Excerpted from Cheung et al. 2012)

Bergman and colleagues (1993) analyzed the activity of m3F8 in an epidural metastatic neuroblastoma model in nude rats using neurological outcome as measured by limb weakness as an endpoint. Paraparesis developed in 79% of rats 19 days post thoracic epidural implantation of human neuroblastoma cells (NMB7). Histological analysis of a single rat on Day 19 showed that the neuroblastoma tumors occupied approximately 50% of the epidural space; the remaining rats began treatment with m3F8 or ^{131}I -m3F8 at the initial sign of weakness with a 2nd dose 5-7 days later before necropsy 10 days post last treatment. Rats receiving no antibody or control antibodies (Table 10) became paraplegic and remained so until death, except for 2 (10%) rats with improvement from Grade 5 limb weakness to Grade 2/3 and no pathological evidence of tumors at necropsy despite evidence of myelopathy. Rats administered intravenous m3F8 (5 mg/kg) later showed improved neurological function (82% vs 10% controls), with initial improvement starting at 3.8 days and maximum improvement by 7.1 days. Six rats receiving m3F8 rats recovered normal neurological function which persisted until necropsy. In rats treated with radiolabeled ^{131}I -m3F8 (5 mCi/kg ^{131}I ~3.125 mCi/mg m3F8), 100% of the treated rats showed improved neurological function from Grade 3.6 to 2.5 by Day 6.8, but 7 out of 9 rats (78%) deteriorated again prior to necropsy. Tumors contained a mean of 1.69% injected dose of ^{131}I -m3F8/g tumor weight (tumor weights ranged from 5 to 21 mg), and tumor to blood ratios varied from 0.7 to 16.2 in individual animals (mean = 4.46).

Table 5-9: Improved limb weakness in rats with epidural neuroblastoma treated with m3F8

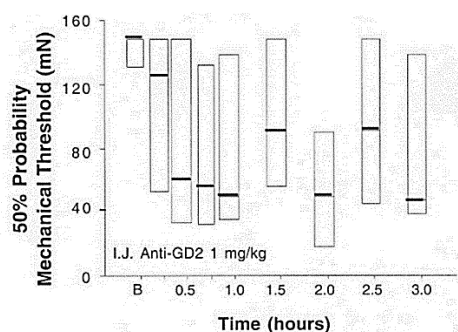
Treatment	# of Rats	Mean Initial Grade of Weakness	# Improved (%)	Median Grade of Weakness following treatment	# With No Tumor at Necropsy
m3F8	17	3.7	14 (82%)	1.5	4 (24%)
^{131}I -m3F8	9	3.6	9 (100%)	2.5	0
Controls	20	3.4	2 (10%)	-	2 (10%)

Controls consisted of no antibody group (n=11), control monoclonal antibody (anti-sheep IgG3, 5 mg/kg, n=4), and radiolabeled (^{131}I) control antibody (n=5). Necropsy evaluation of tumor occurred 10 days post last treatment.

{DANYELZA, naxitamab-gqgk}

The Applicant submitted a series of publications using a surrogate anti-GD2 antibody targeting a separate GD2 epitope from naxitamab to explore naxitamab's known clinical side effect of pain. In Sorkin et al. 2002, (Sorkin LS, 2002) intravenous or intrathecal administration of an anti-GD2 monoclonal antibody (14G2a) to adult Sprague Dawley rats led to mechanical allodynia. Rats treated intravenously with 1 mg/kg of the antibody showed significant decrease in mechanical threshold for paw withdrawal in the 3 hours post administration (Figure 5). This allodynia was, however, limited to mechanical stimulation, as there was no effect on thermal withdrawal threshold following 1 or 3 mg/kg of intravenous anti-GD2 or 0.05 ng of intrathecal anti-GD2 (Figure 6). Control murine IgG2a had no effect on mechanical allodynia.

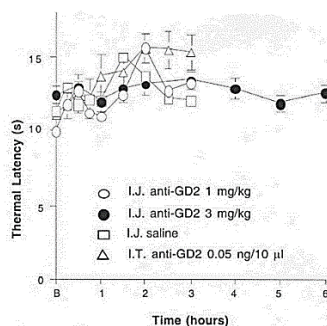
Figure 5: Mechanical threshold for withdrawal in rats treated with an anti-GD2 antibody



(Excerpted from Sorkin et al. 2002)

B-baseline. I.J. – intrajugular administration. mN – bending moment. Time indicates time post injection. Thick lines are median values. A baseline value of 148mN dropped to a low of 48 nM during the 3 hours post dose.

Figure 6: Thermal latency in rats administered intravenous or intrathecal anti-GD2 antibody



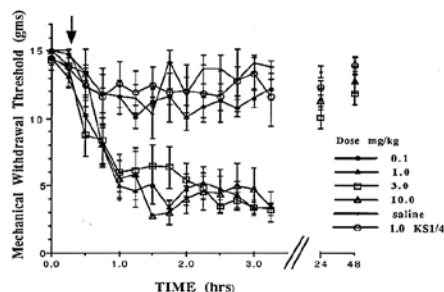
(Excerpted from Sorkin et al. 2002)

In Slart et al. 1997, adult SD rats intravenously (IV) administered chimeric 14.18 (composed of the variable regions of a murine anti-GD2mAb and constant regions of human IgG1k) at doses of 1, 3, or 10 mg/kg led to lower mechanical pain thresholds compared to saline control,

{DANYELZA, naxitamab-gqgk}

starting around 30 minutes post administration (Figure 7). Maximum allodynia occurred 1 hour post administration and increased to up to 73% compared to pre-administration baseline at the 10 mg/kg dose.

Figure 7: Single IV administration of ch14.18 led to lower mechanical pain threshold in adult SD rats



(Excerpted from Slart et al. 1997)

Table 5-10: Percent maximum allodynia in adult SD rats

Dose	Day 1	Day 2	Day 3
Saline	14.4 ± 3.7	10.8 ± 8.9	7.4 ± 5.8
0.1	26.3 ± 2.6*	na	na
1.0	71.1 ± 5.8*	24.3 ± 5.5*	19.1 ± 7.3*
3.0	68.7 ± 5.1*	33.7 ± 10.0*	23.1 ± 11.1*
10.0	72.7 ± 3.7*	26.1 ± 18.0	11.4 ± 4.2
KS1/4 1 mg/kg	20.9 ± 4.5	13.9 ± 6.3	12.3 ± 5.3

Day 1 based on last 2 h of von Frey hair testing (90–195 min). na, not available; day 2 and 3 experiments were not run for this group.

*Denotes significant difference from combined saline group.

(Excerpted from Slart et al. 1997)

Secondary Pharmacology

The Applicant's Position:

Y-mAbs has not conducted any studies dedicated to investigating secondary pharmacodynamics with naxitamab.

The FDA's Assessment:

Relevant pharmacology studies are discussed in the primary pharmacology section. Studies extensively investigating activity unrelated to the antibody target are not commonly expected for monoclonal antibodies.

{DANYELZA, naxitamab-gqgk}

Safety PharmacologyThe Applicant's Position:

In accordance with ICH S9 guidance, Nonclinical Evaluation for Anticancer Pharmaceuticals (October 2009), Y-mAbs has not conducted any standalone safety pharmacology studies with naxitamab.

The FDA's Assessment:

FDA agrees that stand-alone safety pharmacology studies are not expected for an antibody intended for the treatment of patients with advanced cancer. In general cardiovascular, CNS, and respiratory safety endpoints are included in general toxicity studies. See the general toxicity assessment for further details.

5.4.ADME/PKData (presented by Applicant):

Type of Study	Major Findings
Absorption	
No studies were carried out.	
Distribution	
In Vivo Distribution of ¹³¹ I-Naxitamab and ¹³¹ I-mu3F8 in Nude Mice Harboring Human Neuroblastoma Xenografts[14]	Apart from the blood, normal tissues that were among the sites with the highest radioactivity distribution included the spleen (3.9% ID[*]/g), lung (3.5% ID/g), adrenal (3.1% ID/g), bladder (3.1% ID/g), liver (3.0% ID/g), and skin (4.0% ID/g). In tumor tissue, uptake was 29.6% ID/g after ¹³¹I naxitamab administration. These results demonstrate that naxitamab has the desired targeting efficiency for in vivo use as an antitumor immunotherapeutic. <i>*FDA Comment ID=injected dose</i>

{DANYELZA, naxitamab-gqgk}

Type of Study	Major Findings
Metabolism	
No studies were carried out.	
Excretion	
No studies were carried out.	
TK data from general toxicology studies • Hu3F8: A 6-Week Toxicity Study by Intravenous Infusion Administration to Hsd:RH-<i>Foxn1</i>^{nu} nude rats (VB51JD) • Naxitamab: A 13-Week Toxicity Study by Intravenous Infusion Administration to Hsd:RH-<i>Foxn1</i>^{nu} Nude Rats Followed by a 4-Week Recovery Period (YN70HM)	Serum pharmacokinetics were measured after the final intravenous dose of naxitamab in each of Cycles* 1 and 2 of the 6-week study (Study VB51JD) or Cycles 1 and 4 of the 13-week study (Study YN70HM) in athymic Hsd:RH-<i>Foxn1</i>^{nu} nude rats. In both studies, bioanalysis of naxitamab content in rat plasma was measured using a validated ELISA method. In both studies, extent of exposure after treatment was characterized by nonlinear, dose-dependent kinetics over the dose range tested (10-50 mg/kg/d), and exposure in females was 10% to 20% lower than in males. After two cycles of treatment (during Week 1 and Week 5), accumulation of naxitamab exposure was noted in both sexes (1.3- to 1.8-fold in males and 1.2- to 1.3-fold in females). Similar results were observed with four cycles of dosing (during Weeks 1, 5, 9, and 13), with a nonlinear, dose-dependent increase in naxitamab exposure over the dose range tested, which resulted in reduced exposure in general in females compared with males, and moderate systemic accumulation in both sexes after four cycles of treatment

{DANYELZA, naxitamab-gqgk}

Type of Study	Major Findings
	(1.3-fold after Week 13 compared with Week 1 in males at both dose levels and 1.1- to 1.2-fold in females dosed with 10 or 50 mg/kg per occasion, respectively). *FDA Comment: 1 cycle=Days 1, 3, and 5 every 28 days (4 weeks)
TK data from reproductive toxicology studies No studies were carried out.	
TK data from carcinogenicity studies No studies were carried out.	

The Applicant's Position:

The nonclinical pharmacokinetic studies were designed to characterize the absorption and clearance of naxitamab after either single or repeated dosing by intravenous injection in mice and rats and to characterize distribution of naxitamab at target and off-target sites by evaluating immunoreactivity and biodistribution of naxitamab using in vitro and in vivo test methods.

Single-dose pharmacokinetic studies evaluating the absorption and blood clearance of naxitamab were conducted in mice. Total systemic clearance was measured after a single intravenous injection of ¹³¹I naxitamab in C57BL/6 and BALB/c athymic nude mice. Systemic clearance of ¹³¹I naxitamab was substantially faster in nude mice when compared with that in C57BL/6 mice. In a second study, serum pharmacokinetics of naxitamab were investigated after an intravenous injection in nude mice. In this study, the serum terminal half-life of naxitamab was calculated to be 17 hours.

In repeat-dose toxicity studies in nude rats, serum pharmacokinetics were measured after the final intravenous dose of naxitamab in each of Cycles 1 and 2 of a 6-week study or Cycles 1 and 4 of a 13-week study in athymic Hsd:RH-Foxn1^{nu} nude rats. In both studies, the extent of exposure after naxitamab administration was characterized by nonlinear, dose-dependent kinetics over the dose range tested; additionally, after either two or four cycles of treatment with naxitamab, there was evidence of accumulation in the latter dosing cycle. In general, exposure in females was slightly lower than in males.

{DANYELZA, naxitamab-gqgk}

The potential distribution and affinity of naxitamab to organs of interest were evaluated by in vitro and in vivo test methods. In an in vitro tissue immunoreactivity study, the relative affinity of naxitamab was assessed in selected frozen human tissue sections (normal organ and muscle tissue, and neuroblastoma tissues) to better characterize the potential distribution and reactivity of the antibody across tissues of interest. In general, aside from tumor tissues, naxitamab showed relatively strong affinity to the brain, cerebellum, and spinal cord from healthy tissue sections and weak affinity to the lung, sigmoid colon, stomach, and testes. In an in vivo distribution study, a single intravenous dose of ^{131}I naxitamab was administered to athymic nude mice harboring xenografted subcutaneous human neuroblastoma tumors. The mouse model used in the biodistribution study, athymic nude mice harboring subcutaneous human neuroblastoma xenografts, was the same model used for in vivo primary pharmacodynamics studies evaluating the efficacy of naxitamab in an animal model of disease. In distribution studies in mice, naxitamab preferentially accumulated in tumor tissue compared with nontumor tissues.

The FDA's Assessment:

FDA agrees with the Applicant's analysis of distribution of intravenous ^{131}I -hu3F8-IgG1 (naxitamab) and ^{131}I -m3F8 (100 μCi) in adult female athymic nude mice bearing subcutaneous LAN-1 neuroblastoma tumors showing accumulation mostly in tumors (29% of injected dose/gram of mouse), followed by blood, spleen, liver, adrenal, bladder, lung, and skin (2.1-4.2%), though use of a high GD-2 expressing implanted human tumor may exaggerate the distribution of the antibody to tumor vs normal tissue.

FDA could not confirm the difference in absorption and clearance of naxitamab in the C5BL6 vs. nude mouse; however, this data was not critical for the nonclinical safety assessment of this product. Studies investigating metabolism and excretion are not commonly expected for monoclonal antibodies.

FDA agrees that tissue cross reactivity studies showed binding to peripheral nerve, cerebellum, spinal cord, frontal lobe, and pons. Basal epithelium of the skin was another important target in some studies. In additional studies to those discussed above, the Applicant determined the tissue cross-reactivity of naxitamab (hu3F8) in Study #PK86DG and compared the cross-reactivity of naxitamab (hu3F8) and Unituxin (an alternate anti-GD2 antibody targeting a different epitope) in Study #DL25SP using frozen tissues from humans (3 donors), Sprague-Dawley (SD) rats, and Hsd:RH *Foxn1*^{nu} (nude) rats. Tissues were limited to skin containing peripheral nerve, tibial peripheral nerve, cerebellum, spinal cord, frontal lobe, and pons from each species. Positive staining occurred in cerebral cortex, cerebellum, spinal cord, and

{DANYELZA, naxitamab-gqgk}

peripheral nerve tissues for naxitamab from each species, representing on target binding. There were no significant differences in intensity or distribution of the staining between the two antibodies in human tissues. Naxitamab staining in human tissues had increased intensity compared to tissues from either rat strain in both studies. Additional naxitamab staining included basal epithelium of the skin in human tissues and follicular epithelium of the skin in both rat species in both studies. Non-specific staining with naxitamab and Unituxin occurred at levels similar to those that observed with isotype controls in the white matter from neural tissues analyzed from human donors. No non-specific staining occurred in either rat species using naxitamab.

5.5. Toxicology

5.5.1. General Toxicology

Data (presented by Applicant):

Study title/ Study number:

A 13-Week Toxicity Study by Intravenous Infusion Administration to Hsd:RH-*Foxn1*^{nu} Nude Rats Followed by a 4-Week Recovery Period (YN70HM)

Key Study Findings

- The intravenous infusion administration of naxitamab (an anti-GD2 mAb) to Hsd:RH-*Foxn1*^{nu} nude rats, over four cycles of 3 treatment days, up to 50 mg/kg per occasion was generally well tolerated over the 13-week dosing period. Body weight gain was slightly affected with treatment; however, no other treatment-related effects were noted with respect to clinical evaluations (including general health and injection-site examinations), food consumption, nociception response, or ophthalmoscopic examination.
- Treatment-related findings on organ weights and on hematology and blood chemistry parameters were considered nonadverse. In general, these effects were mild, lacking dose-related trends, and reversible.
- Adverse findings in histopathology evaluations of the stomach, including hyperplasia with inflammation in the glandular mucosa of the stomach in males at 50 mg/kg per occasion and marked erosions of the glandular mucosa of the stomach in females at greater than or equal to 10 mg/kg per occasion, resulted in the NOAEL to be established at 10 mg/kg/day (30 mg/kg per cycle) in male rats only, corresponding to a C_{max} of 0.282 mg/mL and AUC_{0-216 h} of 19.9 mg h/mL

{DANYELZA, naxitamab-gqgk}

after four dosing cycles.

FDA Additional Comment on Key Findings: In addition to the findings listed above, histopathology findings of inflammatory cell infiltrates and inflammation occurred in the plantar and tibial nerves.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 10, or 50 mg/kg per occasion.
Dosing on Week 1 (Days 1, 3, 5), Week 5 (Days 29, 31, 33), Week 9 (Days 57, 59, 61), and Week 13 (Days 85, 87, 89)

Route of administration: Intravenous infusion

Formulation/Vehicle: (b) (4) (i.e., Poloxamer 188);
(b) (4) Na-citrate, (b) (4) NaCl, pH 5.7

Species/Strain: Rat/Hsd:RH-Foxn1^{nu}

Number/Sex/Group: 30 male and 30 female (main study);
15 male and 15 female (recovery phase)

Age: 7-8 weeks at the start of treatment

Satellite groups/unique design: None

Deviation from study protocol affecting interpretation of results: No

{DANYELZA, naxitamab-gqgk}

Observations and Results: changes from control

Parameters	Major Findings
Mortality	No treatment-related mortality occurred. There were 7 unscheduled deaths during the study, including 2 control animals, 3 animals that were treated at 10 mg/kg/day, and 2 animals that were treated at 50 mg/kg/day. Of the deaths, 5 occurred during the treatment phase of the study, and 2 occurred during the recovery phase. All were considered incidental and not test article-related.
Clinical Signs	There were no other clinical signs of note, including any from general health examinations or injection site observations, that were considered to be outside of normal limits.
Body Weights	Compared with controls, there was an apparent trend of slower rates of weight gain in naxitamab-treated males at both dose levels (88%-94% of control animal's weight) and in females treated at both dose levels (89%-91% of control animal's weight) from Days 1 to 95 of the study. In the recovery phase, mean weight value gains were also reduced in males treated at either dose level. On the basis of these trends, body weight was considered to be affected by naxitamab treatment.
Ophthalmoscopy	There were no treatment-related ophthalmoscopic findings.
Hematology	Nonadverse, reversible effects on hematology parameters were observed with treatment, including increased reticulocyte counts in females at Week 6 (1.11×) and increased total leukocyte counts in males at both dose levels at Week 6 (1.11-1.32×) and at Week 13 (1.33-1.43×). Dose-related increases in neutrophils, lymphocytes, eosinophils, and basophils were observed in males at Week 6 (1.10-1.73×) and, except for basophils, also at Week 13 (1.16-1.61×). At Week 13, monocytes were also elevated in naxitamab-treated males (1.70-1.87×). Shorter prothrombin times were noted in both sexes and with either dose level at Week 6 (0.96-0.82×) and Week 13 (0.91-0.80×). The hematological effects recovered by the end of the 4-week recovery period after the last cycle of dosing.
Clinical Chemistry	Nonadverse effects on blood chemistry parameters were observed after either two or four dosing cycles. At Week 13, the changes included increased urea concentrations in both sexes at the high dose level (1.12-1.15×) and increased glucose concentrations in males at either dose level (1.16-1.23×). Except for glucose levels in males treated at the high dose of naxitamab, all changes in blood chemistry recovered by the end of the recovery period. The treatment-related

{DANYELZA, naxitamab-gqgk}

	effects were generally mild, not dose related, and not associated with macroscopic or histologic organ findings. FDA Additional Comment: There was a 13% increase in Potassium in HD males at the 6 week timepoint.
Urinalysis	The composition of urine was unaffected by treatment.
Gross Pathology	The macroscopic examination performed in animals after 4 weeks of recovery revealed changes in the stomach. Internal depressions were observed in one female previously treated with 50 mg/kg per occasion, two females previously treated with 10 mg/kg per occasion, and one control female. Thickening of the stomach wall was also observed in one female, which was previously treated with 10 mg/kg per occasion.
Organ Weights	Nonadverse, reversible changes in organ weights were observed, consisting of higher mean adjusted liver weights in males at the high dose level (1.10×), lower mean adjusted thyroid and parathyroid weights at either dose level in both sexes (0.67-0.74× in males, 0.88× in females), and higher spleen weights in females treated at the high dose level (1.16×). Minor changes in reproductive organ weights were observed in both sexes at both dose levels, including increased prostate weights (1.08-1.11×) and decreased seminal vesicle weights (0.89-0.97×) in males and elevated uterus and cervix weights (1.08-1.11×) in females. In general, these findings were not statistically significant and lacked a dose-related trend. Except for the findings in reproductive organs in animals treated at the high dose level, all changes in organ weights recovered 4 weeks after dosing. The persistent, minor changes in reproductive organ weights were of unknown etiology, but they were of small magnitude and were not associated with histological findings, suggesting that the changes were nonadverse.
Histopathology	Treatment-related histopathology changes were confined to inflammatory and/or hyperplastic changes of the glandular mucosa of stomachs in males treated with 50 mg/kg per occasion, and erosions of the glandular mucosa of the stomach in females treated with 10 mg/kg per occasion and in both sexes treated with 50 mg/kg per occasion. In the stomach, erosion of the glandular mucosa mostly correlated with macroscopic depressions of the glandular stomach, and hyperplasia of the glandular mucosa mostly correlated with macroscopic thickening of the mucosa. Erosions of the glandular mucosa were sometimes accompanied by inflammation and/or edema, mostly in the males. After the 4-week off-dose period, there was a full recovery of both the macroscopic and microscopic findings

{DANYELZA, naxitamab-gqgk}

	seen in the stomach in males. In females, there was full recovery of the hyperplasia, inflammation, and edema of the glandular mucosa, and partial recovery of the glandular mucosa erosions.
--	---

FDA Additional Comment on Histopathology (table added by FDA): In addition to the histopathological findings described above, there were occasional findings of inflammation in the nerves in males.

Sex		Males			Females		
Dose (mg/kg)		0	10	50	0	10	50
# main group, # recovery		10,5	9,4	10,4	9,4	10,4	9,5
<i>Nerve, plantar</i>							
Infiltrate, inflammatory cell	Minimal	2,-	-	4,-	-	-	-
	Slight	-	-	1	-	-	-
<i>Nerve, tibial</i>							
Inflammation	Moderate	-	-	1,-	-	-	-

Other Evaluations	Assessment of pain (nociception) response was performed in Study YN70HM. There was no clear effect of treatment on pain threshold on Days 1, 29, and 85 in the animals because the response in the treated animals showed no significant magnitude of change from pretreatment and/or concurrent controls. A statistically significant difference of note was the increased mean values immediately after dosing in Week 1 compared with predose in the treated females. However, because there was considerable overlap of individual values across the groups and no effect in females in Weeks 5 and 13, and no effect in males in Weeks 1, 5, and 13, this finding could not be clearly attributed to treatment.
--------------------------	--

FDA Additional Comment on Toxicokinetics (table added by FDA): Naxitamab C_{max} increased with increased dose, no sex differences in exposure occurred, and exposure as measured by AUC was less than dose proportional.

Dose		10 mg/kg		50 mg/kg	
Parameter	Sex	M	F	M	F
Week 1 (Day 5)					
C _{max} µg/mL		222	220	935	963
AUC ₀₋₂₁₆ µg*h/mL		15200	13400	19900	15000
Week 13 (Day 89)					
C _{max} µg/mL		282	197	1300	1110
AUC ₀₋₂₁₆ µg*h/mL		57700	52200	77800	61100

{DANYELZA, naxitamab-gqgk}

The Applicant's Position:

The Hsd:RH-Foxn1^{nu} nude rat species has been used for the pivotal toxicity studies and toxicokinetic evaluations to mitigate the potential risk of a strong antidrug antibody response, which would limit the value of longer-term chronic toxicity studies in outbred laboratory rat strains (e.g., Sprague-Dawley or Wistar rats). Y-mAbs evaluated on-target tissue reactivity in two GLP-compliant studies by using selected tissues of human and rat origin to support the species selected for toxicology studies (Studies PK86GD and DL25SP). A non-GLP in vitro study comparing the ability of naxitamab to mediate an immune response by cells from nude rats against rat GD2-expressing cells versus human cells against human GD2-expressing cells showed that naxitamab induced ADCC in human and nude rat systems. The binding profile comparisons and the functional assays conducted with cells from the nude rat species, in addition to other factors that substantiate the use of the nude rat species in toxicology studies (e.g., its historical use in regulatory toxicology studies and its retention of intact relevant downstream systems, such as natural killer cells, macrophages, and the complement system), justify the selection of the Hsd: RH-Foxn1^{nu} nude rat species for pivotal toxicity studies and toxicokinetic evaluations.

The safety profile of naxitamab is based on a single-dose toxicity study in mice and repeat-dose toxicology studies (6- and 13-week) in Hsd: RH-Foxn1^{nu} nude rats. In brief, for the repeat-dose studies, in the 6-week study, nonadverse changes in hematological and biochemical parameters and organ weights were observed and considered to be treatment-related; however, these changes were generally minor and were not correlated with macroscopic or microscopic findings. Because all findings were considered incidental or nonadverse in this study, the NOAEL was determined to be 50 mg/kg/day (150 mg/kg per cycle) for both male and female rats, corresponding to a mean (sexes combined) C_{max} of 1.57 mg/mL and AUC_{0-216 h} of 86.15 mg·h/mL after two dosing cycles. In the 13-week study, adverse findings in histopathology evaluations of the stomach resulted in the NOAEL to be established at 10 mg/kg/day (30 mg/kg per cycle) in male rats only, corresponding to a C_{max} of 0.282 mg/mL and AUC_{0-216 h} of 19.9 mg·h/mL after four dosing cycles.

In mice and rats, it was demonstrated that naxitamab had acceptable safety margin estimates based on body weight scaling of the NOAEL to the human equivalent dose. Overall, Y-mAbs asserts that the safety profile of naxitamab established in this focused nonclinical program, particularly in the context of the extensive clinical history of use of naxitamab, murine 3F8, and other anti-GD2 antibodies that demonstrates an adequate safety profile, supports the use of naxitamab for the treatment of neuroblastoma.

{DANYELZA, naxitamab-gqgk}

The FDA's Assessment:

While FDA generally agrees with the Applicant's description of the findings in the nude rat toxicology study, the Agency does not agree that the nude rat adequately recapitulates the critical toxicological attributes of the product to fully inform on the safety of naxitamab. Naxitamab-mediated toxicities in the nude rat in the 13-week study were generally minor with mild GI toxicity (decreased weight gain, minimal to moderate histopathological erosion in the glandular stomach), decreased thyroid weight, and an increased incidence of inflammation of nerves (male rats only). Similar clinical signs and pathology occurred in a 6-week intravenous GLP-compliant study in nude rats conducted by the Sponsor in which naxitamab was administered at 0, 10, or 50 mg/kg for 2 cycles (Week 1; Days 1, 3, 5 and Week 5; Days 29, 31, 33) including decreased weight gain, hematology and clinical chemistry changes, and histopathology. Evaluation of nociception via foot pinch indicated no change in pain threshold following mechanical stimulation with a blunt pointer at any dose level, as observed in the 13-week study.

While nude mice and rats are common strains employed for pharmacological activity assessment of drugs, particularly in tumor implantation models, they are not typically used as the primary model for the toxicological safety assessment of either drugs or biologics. The Applicant explained that the NK cells, neutrophils, and macrophages that drive the killing of naxitamab-bound cells are present in nude rats and that, therefore, the use of this strain would permit for a reasonable safety assessment in rodents even in chronic toxicity studies as the animals would not develop anti-product antibodies that would limit exposure to the test-article. FDA acknowledged both that these cells were present and the Applicant's goal of circumventing the development of anti-drug antibodies, but expressed some reservations regarding the use of an immune deficient model to model the safety of a product with a mechanism of action based on immune-mediated cell killing and suggested that the Applicant conduct an in vitro study comparing the ADCC activity of naxitamab in a nude rat system vs. a human system at several points during the clinical development of the product to help support the use of this model. The Applicant has provided this data with the BLA submission; however, the data shows minimal activity using nude rat cells vs. human cells as effector cells. This data, in addition to the lack of effects on nociception demonstrated in the nude rat, suggests that this strain does not adequately recapitulate the toxicity of naxitamab. Literature cited by the Applicant using other antibodies targeting GD2 in fully immunocompetent rat or mouse models demonstrates the ability of these rodents to model the allodynia observed clinically, further suggesting that though some immune-competent rodent models may adequately predict the toxicity of the antibody the nude rat is does not, making it an inadequate toxicology model for this product.

{DANYELZA, naxitamab-gqgk}

General toxicology; additional studies

Data (Applicant presented):

Study title/Study number: Naxitamab: Preliminary Juvenile Toxicity Study in the Hsd:RH-Foxn1^{nu} Nude Rat by Intraperitoneal Injection and Intravenous Infusion Administration (CB61CK)

Key Study Findings

- Treatment with naxitamab at dose levels up to and including 50 mg/kg/occasion was well tolerated. No premature deaths occurred during the course of the study, and there were no changes in general clinical condition or postdosing signs that were related to naxitamab administration.
- There were no macroscopic abnormalities that were clearly attributable to naxitamab administration and no histopathological changes were apparent in the stomach of animals given 50 mg/kg per occasion.
- On the basis of the results obtained in this study, it was concluded that the dose level of 50 mg/kg per occasion (limited by the maximum volume/infusion rate in the required dose duration) would be suitable for use as the high dose level in a main juvenile toxicity study, if deemed applicable.

Conducting laboratory and location: (b) (4)

GLP compliance: No

Methods

Dose and frequency of dosing:	0, 5, 7.5, 10, 30, or 50 mg/kg per occasion. Days 1, 3, and 5 (PND 12, 14, and 16), and on Days 29, 31, and 33 (PND 40, 42, and 44).
Route of administration:	Intraperitoneal injection (Cycle 1) and intravenous infusion (Cycle 2)
Formulation/Vehicle:	(b) (4) (i.e., Poloxamer 188); (b) (4) Na-citrate, (b) (4) NaCl, pH 5.7
Species/Strain:	Rat/Hsd:RH-Foxn1 ^{nu}
Number/Sex/Group:	23 male and 21 female
Age:	PND 12 at the start of treatment
Satellite groups/unique design:	None

{DANYELZA, naxitamab-gqgk}

Deviation from study protocol No
affecting interpretation of results:

Observations and Results: changes from control

Parameters	Major Findings
Mortality	No premature deaths occurred during the course of the study.
Clinical Signs	There were no changes in general clinical condition or postdosing signs that were related to naxitamab administration.
Body Weights	Group mean body weight gain for females given naxitamab at 50 mg/kg per occasion during the two dosing cycles was slightly lower than control animals, with statistical significance attained for the differences during both dosing cycles. The body weight gain of males given 50 mg/kg per occasion was slightly lower than control animals during the intraperitoneal dosing cycle, but statistical significance was not attained. Overall mean body weight gain in both sexes in this dose group during PND 12-54 was unaffected. The body weight performance of males and females given 5-/7.5/10 or 30 mg/kg per occasion was unaffected.
Gross Pathology	At scheduled termination on PND 54, one male in the 30-mg/kg per occasion group and one female in the 5-/7.5-/10-mg/kg per occasion group had diffuse dark areas in the glandular mucosa of the stomach. In addition, one male in the 50-mg/kg per occasion group and one female in the 5-/7.5-/10-mg/kg per occasion group had a liver mass.
Histopathology	Microscopic examination of the stomach of animals in the control and 50-mg/kg per occasion groups revealed no test item–related findings. The incidence and distribution of all findings were considered to be unrelated to treatment.
Other Evaluations	The pain threshold of males was not clearly affected by naxitamab, although it was noted during the predose assessment that the pain threshold of males in the 50-mg/kg per occasion group was reached at a slightly lower force (50 g) than in controls (59 g). In females, while there was no effect on pain threshold during the predose assessment, following dose administration there was a clear and dose-dependent decrease in pain threshold in the 30- or 50-mg/kg per occasion groups.

{DANYELZA, naxitamab-gqgk}

	There was no clear evidence of an effect of naxitamab administration on the age or body weight of attainment of sexual maturation.
--	--

The Applicant's Position:

This preliminary study assessed the influence of naxitamab, when administered to juvenile Hsd:RH-Foxn1^{nu} nude rats at doses up to 50 mg/kg per occasion from PND 12 over two cycles of 3 treatment days: on Days 1, 3, and 5 (PND 12, 14, and 16) by intraperitoneal injection, and on Days 29, 31, and 33 (PND 40, 42, and 44) by intravenous infusion for up to 60 minutes.

Based on the results obtained in this study, it was concluded that the dose level of 50 mg/kg per occasion (limited by the maximum volume/infusion rate in the required dose duration) would be suitable for use as the high dose level in a main juvenile toxicity study, if deemed applicable.

The FDA's Assessment:

FDA did not review this study in detail because it was a dose range finding study using a limited number of animals in a strain that does not appear to be a model that adequately recapitulates the toxicity of naxitamab and did not include the primary histopathology data. No deaths or clinical observations occurred in this study, with the exception of decreased body weight gain in the high dose group. No changes in pain thresholds were present in males and effects in females were too highly variable to make any conclusions.

5.5.2. Genetic Toxicology

The Applicant's Position:

Y-mAbs has not conducted genetic toxicology studies with naxitamab. In accordance with ICH S6 and ICH S9, these studies are not considered necessary to support a marketing application for a biotechnology-derived pharmaceutical intended to treat advanced cancer.

The FDA's Assessment:

FDA agrees.

{DANYELZA, naxitamab-gqgk}

5.5.3. Carcinogenicity

The Applicant's Position:

Y-mAbs has not conducted carcinogenicity studies with naxitamab. In accordance with ICH S6 and ICH S9, these studies are not considered necessary to support a marketing application for a biotechnology-derived pharmaceutical intended to treat advanced cancer.

The FDA's Assessment:

FDA agrees.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Considering the proposed patient population, it is unlikely that reproductive and developmental studies in animals will contribute meaningful safety data relevant to the indicated population; therefore, Y-mAbs has not conducted reproductive toxicology studies with naxitamab.

The FDA's Assessment:

No reproductive and developmental toxicology studies were conducted to support the submission of the BLA for naxitamab. Based on the age of the proposed patient population, FDA agreed that traditional reproductive toxicology studies were not warranted to support the use of this product in the treatment of patients with maintenance phase of high-risk neuroblastoma, as based on a review by Brodeur and Maris 2003, neuroblastoma is defined as a pediatric cancer, with the average age of diagnosis being 18 months with about 40% of patients diagnosed by 1 year of age, 75% by 4 years and 98% by 10 years of age.

{DANYELZA, naxitamab-gqgk}

5.5.5. Other Toxicology Studies

Applicant's Position:

Y-mAbs did not conduct any other toxicology studies with naxitamab.

The FDA's Assessment:

Tissue cross-reactivity studies of naxitamab (hu3F8) using frozen tissues from humans, Sprague-Dawley (SD) rats, and Hsd:RH *Foxn1*^{nu} (nude) rats are discussed in the pharmacokinetic section of this Assessment Aid.

X Stephanie L. Aungst

Primary Reviewer

X Whitney S. Helms

Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The proposed dosing regimen for naxitamab is 3.0 mg/kg/day on Days 1, 3, and 5 of each 28-day cycle, for a total of 9 mg/kg/cycle, in combination with GM-CSF 250 µg/m²/day on Days -4 to 0 and 500 µg/m²/day on Days 1 to 5 of each 28-day cycle. The primary efficacy endpoint (ORR) of this dosing regimen was evaluated in Study 12-230, Study 201, and Study 2PR01. The safety of this dosing regimen was supported by data from Study 12-230, Study 201, Study 2PR01, Study 11-009, and Study 12-116. Of these studies, 12-230, 11-009 and 12-116 were conducted by Memorial Sloan Kettering Cancer Centers (MSKCC), while 201 and 2PR01 were conducted by the Applicant.

FDA recommends a dose cap for patients with a body weight (BW) > 50 kg, with a maximum naxitamab dose of 450 mg/cycle. The dose cap is based on the pharmacokinetic characteristics of naxitamab and the relationships between naxitamab exposure and efficacy/safety. Naxitamab exposure is predicted to increase with increasing BW using per kg dosing. The exposure-response relationship for safety suggests higher safety risks (bronchospasm, hypotension, and hypertension) for patients with higher naxitamab exposures, while for efficacy, no significant relationships between naxitamab exposure and ORR/complete response. The exposure-response analysis for efficacy is based on the limited data from the trials and in small number of patients with potential confounding factors (e.g., ADA effect).

The immunogenicity data from studies 12-230, 11-009 and 12-116 conducted by MSKCC are deemed unreliable as the anti-drug-antibody (ADA) assays used in these trials were not validated. Study 201, conducted by the Applicant, using validated ADA assays only tested 23 patients. Therefore, the following postmarket commitment (PMC) will be issued:

Conduct immunogenicity testing in all patients enrolled in the ongoing Study 201 and any planned clinical trial(s) of naxitamab using the validated assays to adequately characterize the incidences of anti-drug antibody (ADA) and neutralizing antibody against naxitamab. Assess the impact of ADA on the pharmacokinetics (PK), safety and efficacy of naxitamab to inform naxitamab labeling. Refer to the following FDA Guidance for Industry: "Immunogenicity Assessment for Therapeutic Protein Products" available at <https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf>.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The PK data support the use of naxitamab for the treatment of refractory or relapsed high-risk neuroblastoma in bone and/or bone marrow in combination with GM-CSF. The pharmacokinetic evaluations are based on data from subjects treated with naxitamab for high-risk neuroblastoma or other GD2-positive tumors within a clinical trial dose-escalation setting. The pharmacokinetic properties of naxitamab have been characterized by data from single doses and multiple doses across a range of dose regimens (including the proposed dose regimen) as well as from population pharmacokinetic analyses. The analyses included dose-exposure characterization and intrinsic factor evaluation. The proposed dosing regimen was further supported by efficacy and safety evaluations.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the PK data support the use of naxitamab for the treatment of refractory or relapsed high-risk neuroblastoma in bone or bone marrow, in combination with GM-CSF. Of note, only the PK data from Study 201 are deemed reliable because the PK assays used in other studies, including studies 12-230, 11-009, and 12-116, were not fully validated.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The proposed dosing regimen was based on a clinical judgement during the dose-escalation part of Trial 12-230 (see Section 8.1.1).

The FDA's Assessment:

The FDA agrees with the Applicant's position. Trial 12-230 evaluated naxitamab doses of 0.3, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2 mg/kg QD administered on Day 1, 3, and 5 of each 28-day cycle in the Phase 1 portion of the trial and evaluated naxitamab 3.0 mg/kg QD on Day 1, 3, and 5 of each 28-day cycle in the Phase 2 portion of the trial. Results of this trial suggested that ORR was comparable across the different dose levels in Phase 1 and a higher complete response (CR) rate was observed in the 3 mg/kg group from Phase 2 based on cross-phase comparison. The MTD was not reached during the trial. However, a greater

{DANYELZA, naxitamab-gqgk}

percentage of patients in the 2.6 to 3.2 mg/kg dose group reported ≥ 1 related Grade 3+ treatment-emergent adverse events (TEAE) (71%, 15/21) and ≥ 1 related serious adverse events (SAE) (38%, 8/21) compared to those in patients in the lower dose groups (39%, 14/36 Grade 3+ TEAE; 22%, 8/36 ≥ 1 related SAE). The proposed dosing regimen of 3.0 mg/kg (9.0 mg/kg per cycle) is generally acceptable based on benefit-risk evaluation from Trial 12-230, 201, and 2PR01; however, FDA recommends a dose cap for body weight (BW) >50 kg (see Section 6.2.2.2 and Section 6.3.2.2 for detailed information).

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors and DDI considerations, as further detailed in Sections 6.3.2.3 and 6.3.2.4.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that no therapeutic individualization is needed in the proposed indication based on DDI considerations. However, FDA recommends a dose cap for BW >50 kg since naxitamab exposure is predicted to increase with increasing BW using a per kg dosing regimen and the exposure-response relationship for safety suggests higher safety risks (bronchospasm, hypotension, and hypertension) for patients with higher naxitamab exposures.

6.2.2.3. Outstanding Issues

The Applicant's Position:

There are no outstanding issues.

The FDA's Assessment:

FDA disagrees with the Applicant's position of no outstanding clinical pharmacology issues precluding approval of this application. FDA will issue a PMC requesting the Applicant to adequately characterize naxitamab immunogenicity using fully-validated assays in the ongoing Study 201 and any planned clinical trial(s) of naxitamab, and assess the impact of ADA on the PK, safety and efficacy of naxitamab to inform naxitamab labeling.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

The PK of naxitamab has been evaluated in four clinical trials in patients. MSK evaluated the PK of naxitamab in three trials (Trials 11-009, 12-116, and 12-230) as part of a dose-escalation setting using a partially validated assay developed by MSK. Y-mAbs investigated the PK of naxitamab with the proposed dose regimen in Trial 201 using a fully validated assay. In addition, a population PK analysis of naxitamab was performed using data from these 4 trials to characterize the PK after single and multiple doses in subjects with high-risk neuroblastoma and to explore the impact of subject demographics and intrinsic factors on relevant PK parameters.

Naxitamab is administered by intravenous infusion only. There appeared to be a rapid distribution phase during the first 48 hours after each infusion compared with the observed terminal elimination phase after the third infusion. In the population PK analysis, the terminal half-life was estimated to be 197 hours (8.2 days). Naxitamab exposure is therefore expected to be comparable across cycles with 4 to 8 weeks between cycles. This is also in line with the limited accumulation from one cycle to the next that has been observed in the precycle trough concentration levels in Trial 201.

The dose-escalation trials (Trials 11-009, 12-116, and 12-230) generally showed that naxitamab exposure (C_{max} and AUC) increased approximately linearly with increasing dose within each trial. The population PK analyses confirmed the dose proportionality seen in the individual trial analyses.

The FDA's Assessment:

FDA generally agrees with the Applicant's position on the general pharmacology and pharmacokinetic characteristics of naxitamab. Of note, FDA calculated the terminal half-life of naxitamab based on the PK data from Cycle 1 in Trial 201, as Trial 201 is the only trial that used the fully validated assay in the naxitamab concentration measurement.

{DANYELZA, naxitamab-gqgk}

6.3.2. Clinical Pharmacology Questions

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

The Applicant's Position:

The clinical pharmacology program did not comprise specific supportive effectiveness evaluations.

The FDA's Assessment:

An exposure-response analysis for efficacy was conducted by the Applicant in response to FDA's information request. FDA generally agrees with the Applicant's position that no significant relationships were identified between naxitamab exposure and ORR/CR, as detailed in Section 19.4.2. Of note, the exposure-response analysis examining the relationship between naxitamab exposure and ORR/CR was conducted using limited data from the trials in a small number of patients with potential confounding factors (e.g., ADA effect).

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

The Applicant's Position:

The proposed dosing regimen has proven effective with manageable side effects in patients with neuroblastoma, as detailed in Sections 8.1 and 8.2. Robustness of the results was further evident from the subgroup analyses, as detailed in Sections 6.3.2.3 and 8.1.8.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. No significant relationships between naxitamab exposure and ORR were identified; however, the exposure-response relationship for safety suggests higher safety risks (Grade 2+ bronchospasm, hypotension, and hypertension) for patients with higher naxitamab exposures, as detailed in Sections 19.4.2 and 19.4.3.

The Applicant proposed a naxitamab dosage of 3 mg/kg/day on Days 1, 3, and 5, for a total dose of 9 mg/kg per cycle. Population PK analysis identified the effect of body weight on naxitamab exposure with higher exposure at higher body weights. Naxitamab exposure was simulated with the proposed dosing regimens across the relevant body weight range (10 –

{DANYELZA, naxitamab-gqgk}

80 kg) using the final population PK model, as detailed in Section 19.4.1.

Table 6-1. Summary of simulated naxitamab clearance and AUC_{0-672h} versus bodyweight

WT group	Total dose	n	Clearance (mL/h)		AUC _{0-672h} (μg·h/mL)	
			mean	90% CI	mean	90% CI
10-20 kg	90-180 mg	500	38.7	22.8 - 61.5	3.52·10 ³	2.06·10 ³ - 5.44·10 ³
20-30 kg	180-270 mg	500	46.5	27.8 - 72.0	4.84·10 ³	2.94·10 ³ - 7.13·10 ³
30-40 kg	270-360 mg	500	50.7	31.0 - 77.8	6.13·10 ³	3.70·10 ³ - 8.99·10 ³
40-50 kg	360-450 mg	500	55.5	30.7 - 88.2	7.21·10 ³	4.38·10 ³ - 1.11·10 ⁴
50-60 kg	450-540 mg	500	59.6	34.1 - 94.4	8.14·10 ³	4.85·10 ³ - 1.22·10 ⁴
60-70 kg	540-630 mg	500	62.8	36.6 - 96.7	9.09·10 ³	5.55·10 ³ - 1.33·10 ⁴
70-80 kg	630-720 mg	500	66.1	37.4 - 103	9.96·10 ³	6.06·10 ³ - 1.51·10 ⁴

Simulated Naxitamab exposure by weight group for the final PopPK model. n: Number of subjects; CI: Confidence interval.

Source: The Applicant's population PK report (hu3F8-MS-02), Page 59, Table 11.

As shown in Table 6-1, mean predicted AUC_{0-672h} is nearly doubled in patients with BW 70-80 kg compared to patients with a BW of 20-30 kg. Flat dosing in adults and adolescents with higher BW will minimize PK variability. There is limited clinical safety experience in patients with BW > 50 kg at naxitamab doses > 450 mg per cycle (i.e., 3 patients with BW >50 kg received a dose >450 mg/cycle, with 2 patients receiving 3 infusions and 1 patient receiving 5 infusions). Patients with BW >50 kg receiving 3 mg/kg dose are expected to have higher exposures than that observed in the clinical trials. Therefore, based on exposure-matching, the recommended dosage of naxitamab is 3 mg/kg/day up to 150 mg per day on Days 1, 3, and 5, for a total dose of 9 mg/kg up to 450 mg per cycle.

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

The Applicant's Position:

On the basis of the assessment of a potential impact of intrinsic factors on the PK of naxitamab, no dose adjustment or change in dosing regimen is required to accommodate demographic characteristics or special populations.

The effect of intrinsic factors such as body weight, body mass index, body surface area, lean body mass, race, gender, age, and renal or hepatic function was evaluated in the population PK analysis (Study hu3F8-MS-02). Only body weight was retained as a significant covariate, and exposure was predicted to increase with increasing body weight. However, an assessment of

{DANYELZA, naxitamab-gqgk}

TEAEs, infusion-related TEAEs, and SAEs by body weight (<20 kg, 20 to <50 kg, and ≥50 kg) did not indicate increasing toxicities with increasing body weight. In addition, no safety concerns emerged from analyses of TEAEs across gender, race, prior anti-GD-2 therapy, or ADA status (Section 8.2.7).

Finally, efficacy analyses across subgroups by baseline disease status (primary refractory disease vs. incomplete response to salvage treatment), disease compartment (bone vs. bone marrow), age, body weight, prior GD2 therapy, and ADA status have shown consistent efficacy of naxitamab, which supports the premise that no dose adjustments are required based on demographics or for special populations (Section 8.1.8).

The FDA's Assessment:

The FDA disagrees with the Applicant's position that no dose adjustments are required based on demographics or for special populations. FDA recommends a dosing cap (150 mg per day and 450 mg per cycle) for patients with BW >50 kg as described above in Section 6.3.2.2.

In addition, the FDA disagrees with the Applicant's position regarding ADA status since immunogenicity data from studies 12-230, 11-009 and 12-116 conducted by MSKCC are deemed unreliable as the anti-drug-antibody (ADA) assays used in these trials were not validated. Study 201, conducted by the Applicant using validated ADA assays, only evaluated ADA in 23 patients. As such, the FDA will issue a PMC to gather additional ADA and PK data to adequately assess the incidence of ADA and the impact of ADA status on the PK, safety and efficacy of naxitamab.

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

The Applicant's Position:

No formal drug-drug interaction studies have been performed. This is considered acceptable because it is unlikely that naxitamab will interact with concomitant drugs in a way that will affect the systemic exposure of either naxitamab or concomitant drugs for the following reasons:

- While nonprotein drugs are metabolized via the cytochrome P-450 system and/or renal or biliary excretion, an antibody like naxitamab, being a protein, is eliminated via different mechanisms: cellular uptake followed by proteolytic degradation and via

{DANYELZA, naxitamab-gqgk}

interaction between antibody and its target.

- Metabolic competition between antibodies and other proteins have not been described. Furthermore, interaction at the binding target (GD2) between nonprotein drugs or other protein drugs and naxitamab is unlikely.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

X

X

Catharine Bulik, Pharm.D.
Primary Reviewer

Hong Zhao, Ph.D.
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Trials

The Applicant's Position:

All trials pertinent to the evaluation of efficacy and safety of naxitamab for the treatment of high-risk refractory or relapsed neuroblastoma in bone and/or bone marrow in combination with granulocyte-monocyte colony stimulating factor (GM-CSF) are summarized in Table 7-7-1.

The FDA's Assessment:

FDA agrees with the overview of clinical trials used to support the evaluation of efficacy and safety of naxitamab in this BLA. The primary efficacy and safety data are derived from Trials 12-230 and 201. Given several limitations of the other trials, including use of a different dose or regimen of naxitamab, use in patients with different tumor types, or in the case of Study 2PR01, the retrospective nature of the data, information derived from these trials were supportive only.

{DANYELZA, naxitamab-gqgk}

Table 7-1-1 Listing of Clinical Trials Relevant to Naxitamab BLA

Trial Identity NCT Number	Trial Design	Dose Regimen	Trial Endpoints	Naxitamab Treatment Duration/ Follow Up	Number of Patients Enrolled	Trial Population	Number of Sites and Countries
<i>Trials to Support Efficacy and Safety</i>							
12-230 NCT01757626	Single center Phase 1: single-arm, nonrandomized, open-label, dose-escalation (3 + 3) trial Phase 2: single-arm, nonrandomized, open-label trial	<u>Phase 1:</u> - i.v. naxitamab: Days 1, 3, and 5 at 0.9 to 9.6 mg/kg per cycle - s.c. GM-CSF: Days –4 to 0 at 250 µg/m²/d; Days 1 to 5 at 500 µg/m²/d <u>Phase 2:</u> - i.v. naxitamab: Days 1, 3, and 5 at 9.0 mg/kg per cycle - s.c. GM-CSF: Days –4 to 0 at 250 µg/m²/d; Days 1 to 5 at 500 µg/m²/d	<u>Phase 1 Primary:</u> Establish MTD of naxitamab with GM-CSF <u>Phase 1 Secondary:</u> PK <u>Phase 2 Interim Primary:</u> ORR in enrollments with primary refractory or incomplete response to salvage therapy <u>Phase 2 Interim Secondary:</u> DoR, ADA, safety	Median number of cycles initiated in Phase 1, Phase 2, Primary Analysis Set, and All Enrollments were 4.0, 4.0, 6.0, and 4.0 cycles, respectively.	Phase 1: 57 Enrollments Phase 2: 74 Enrollments Safety: 117 unique subjects Efficacy: FAS – 60 enrollments PAS – 45 enrollments	Subjects with refractory or relapsed high-risk neuroblastoma (Phase 1 and Phase 2, Groups 1 and 3) and subjects with a second or greater complete remission at high risk for relapsed (Phase 2, Group 2).	1, U.S.

{DANYELZA, naxitamab-gqgk}

Trial Identity NCT Number	Trial Design	Dose Regimen	Trial Endpoints	Naxitamab Treatment Duration/ Follow Up	Number of Patients Enrolled	Trial Population	Number of Sites and Countries
201 NCT03363373	Multicenter, single-arm, nonrandomized, open-label trial	- i.v. naxitamab: Days 1, 3, and 5 at 9.0 mg/kg per cycle - s.c. GM-CSF: Days -4 to 0 at 250 µg/m²/d; Days 1 to 5 at 500 µg/m²/d	Interim Efficacy Endpoints: ORR, DoR	Mean (SD) number of treatment cycles was 4.6 (2.46), ranging from 1 to 8 cycles.	Enrolled: 25 Cohort 1: 24 Cohort 2: 1	High-risk neuroblastoma with primary refractory or incomplete response to salvage treatment in bone and/or bone marrow	3, U.S., Spain
2PR01 Not Applicable	Retrospective, noninterventional, noncomparative, observational, single-site study	Named patient use; subjects treated 01 Jun 2017 to 30 Nov 2018 Treatment followed one of the protocols: 12-230 201 17-251	ORR, DoR Response in MRD	Median number of cycles initiated in Categories 1 and 2, 3, 4, 5, 6-8, and all categories were 5, 3, 3, 1.5, 4, and 3 cycles, respectively	Enrolled: 63 Category 1: 6 Category 2: 13 Category 4: 27 Category 5: 4 Categories 6-8: 13	High-risk neuroblastoma	1, Spain
<i>Trials to Support Safety</i>							
11-009 NCT01419834	Single-arm, nonrandomized, open-label, dose- escalation (3+3)	- i.v. naxitamab: Days 1 and 8 at 0.06 to 3.0 mg/kg per cycle - Amended to naxitamab: Days 1, 3, and 5 at 3.0 to 9.0 mg/kg per cycle	<u>Primary:</u> Establish MTD <u>Secondary:</u> PK	Median number of cycles initiated for 0.06 to 1.5, 1.6 to 2.4, and 2.6 to 3.0 mg/kg dosage groups were 5.5, 3.0, and 2.0 cycles, respectively.	91 Enrolled SAF: 67 treated with naxitamab	Subjects with refractory or relapsed neuroblastoma or other GD2-positive tumors	1, U.S.

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761171}

{DANYELZA, naxitamab-gqgk}

Trial Identity NCT Number	Trial Design	Dose Regimen	Trial Endpoints	Naxitamab Treatment Duration/ Follow Up	Number of Patients Enrolled	Trial Population	Number of Sites and Countries
12-116 NCT01662804	Single-arm, nonrandomized, open-label, dose- escalation (3+3)	- i.v. naxitamab: Days 1 and 8 at 0.3 to 1.2 mg/kg per cycle - s.c. IL-2: Days 8 to 12 at 6×10^6 U IL-2/m²/d	<u>Primary:</u> Establish MTD of naxitamab when administered with IL-2 <u>Secondary:</u> PK in presence of IL-2	Median number of cycles initiated for 0.3, 0.6, 0.9, and 1.2 mg/kg dosage groups was 1.0, 1.0, 4.0, and 2.0 cycles, respectively.	28 enrolled SAF: 12 treated with naxitamab	Subjects with high-risk neuroblastoma or other GD2-positive tumors	1, U.S.

MTD = maximum tolerated dose; FAS = full analysis set; PAS = primary analysis set; SAF = safety analysis set; ADA = anti-drug-antibody; DoR = duration of response; ORR = overall response rate; MRD = minimal residual disease; PK = pharmacokinetics.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Position:

The efficacy evaluation for the BLA is based on an interim analysis of all efficacy data from the pivotal Trial 12-230 at the data cutoff date. Trial 201 and the retrospective Study 2PR01 provide supporting efficacy data.

- Subjects could enroll to Trial 12-230 more than once and could have different disease profiles at different enrollments. Therefore, they are counted by enrollment for the efficacy analysis, and the term “enrollments” is used in place of “subjects.”
- Trial 201 provides interim data for enrollments with at least 1 follow-up for assessment of efficacy endpoints. Subjects could only enroll once in this trial.
- The retrospective Study 2PR01 provides medical record data from patients treated with naxitamab in combination with GM-CSF under compassionate use in Spain.

8.1.1. Trial 12-230

The Applicant's Description:

Trial Design

Basic Trial Design

The pivotal Trial 12-230 was an open-label, single-center trial including subjects with either primary refractory disease or incomplete response to salvage treatment. The trial also included subjects with other disease status at baseline, but they were not included in the efficacy analysis.

Trial 12-230 had two phases. Phase 1 was a single-center, single-arm, open-label, 3 + 3 dose-escalation design. Phase 2 was a single-center, single-arm, nonrandomized, open-label trial.

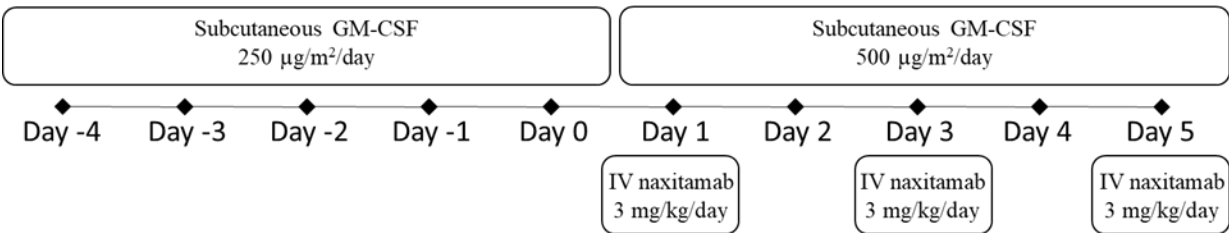
Phase 1 assessed escalating doses of intravenous (i.v.) naxitamab infusions (Days 1, 3, 5) in combination with subcutaneous (s.c.) GM-CSF (Day –4 through 5) during a 10-day cycle repeated every 2 to 4 weeks. Subjects with no dose-limiting toxicity (as defined in protocol) and no progression of disease during the first cycle had the option of receiving an additional 3 cycles if antidrug antibody (ADA) titer was negative. Subjects who completed 4 cycles of treatment

{DANYELZA, naxitamab-gqgk}

without complications or disease progression had the option of continuing treatment for up to 24 months from their first dose of naxitamab.

In Phase 2 all subjects receiving naxitamab at 9.0 mg/kg per cycle. Dosing with naxitamab occurred on Days 1, 3, and 5 of each cycle in the presence of s.c. GM-CSF (Days –4 through 5). Cycles were repeated monthly through 5 cycles, then every 1 to 2 months for up to 24 months from trial enrollment or until a subject had received five cycles after a CR or PR was achieved, whichever came first. The basic Phase 2 dosing design is shown in Figure 8-1. The timing of naxitamab and GM-CSF administration was the same in Phase 1.

Figure 8-1 Basic Trial Design



Trial Location

The trial is a single-center trial conducted in New York City, New York, United States.

Choice of Control Group

Since high-risk neuroblastoma is a rare disease, the trial is single-arm with no comparator.

Diagnostic Criteria

The trial enrolled subjects with neuroblastoma diagnosed by 1) histopathology or 2) bone marrow metastases or MIBG-avid lesion(s) plus high urine catecholamine levels.

Key Inclusion/Exclusion Criteria

Enrollment was open to subjects older than 1 year of age with a diagnosis of neuroblastoma, as defined in the section on diagnostic criteria above. Subjects must have had high-risk neuroblastoma (including MYCN-amplified stage 2/3/4/4s of any age and MYCN-nonamplified Stage 4 in subjects greater than 18 months or age). Phase 1 subjects must have had refractory or relapsed neuroblastoma that was resistant to standard therapy (standard therapy included

{DANYELZA, naxitamab-gqgk}

intensive induction chemotherapy, followed by a variety of consolidation or salvage therapies, depending on response). Phase 2 subjects must have had primary or secondary refractory disease in bone or bone marrow, defined as morphologic evidence of neuroblastoma in bone marrow and/or abnormal ^{123}I -MIBG uptake in osteomedullary sites, or had to be in second or greater complete response as defined by INRC with ^{123}I -MIBG findings quantitated by Curie scores. Prior treatment with other anti-GD2 antibody therapies, including murine 3F8, naxitamab, ch14.18, and hu14.18 was allowed. No chemotherapy or immunotherapy for a minimum of 3 weeks prior to start of naxitamab was allowed. Moreover, white blood cell (WBC) count greater than or equal to 1000/ μL , absolute neutrophil count greater than or equal to 500/ μL , absolute lymphocyte count greater than or equal to 500/ μL , and platelet count greater than or equal to 25,000/ μL were required.

Subjects were excluded for existing major organ dysfunction greater than CTCAE Grade 2, with the exception of hearing loss and hematologic toxicity (defined as suppression of all subtypes of WBCs, red blood cells, and platelets); active life-threatening infection; history of allergy to mouse proteins; anti-human anti-GD2 antibody (ADA) titer greater than 1,300 ELISA U/mL, and history of allergy to GM-CSF.

Dose Selection

Phase 1 assessed escalating doses of intravenous naxitamab infusions (Days 1, 3, 5) in combination with s.c. GM-CSF (Day -4 through 5). Dose levels were 0.3 to 3.2 mg/kg/d (0.9 to 9.6 mg/kg per cycle). Subjects came off trial if they had a dose-limiting toxicity, as defined in the protocol, during the first cycle.

Although a maximum tolerated dose was not attained in Phase 1, 9.0 mg/kg per cycle was selected for further development and implemented in Phase 2 of the trial: Intravenous naxitamab infusions (Days 1, 3, 5) of 3.0 mg/kg per infusion in combination with s.c. GM-CSF (Day -4 through 5). The choice of 3.0 mg/kg per infusion (9.0 mg/kg per cycle) as the optimal dose for the Phase 2 part and for further clinical development of naxitamab was a clinical judgement based on the evaluation of the clinical pharmacokinetics, efficacy, safety, and tolerability at that time (i.e., including the investigator's clinical judgement of each subject case based on individual subject details).

Trial Treatments, Treatment Assignment, and Blinding

Trial 12-230 was an open-label, single-arm trial.

Each subject received naxitamab with GM-CSF over a 10-day period in a cycle. A cycle started with 5 days of GM-CSF administered s.c. at 250 $\mu\text{g}/\text{m}^2/\text{d}$ before the start of naxitamab infusions

{DANYELZA, naxitamab-gqgk}

(Day -4 to Day 0) (Figure 8-1). On Days 1 through 5, GM-CSF was administered at a dose of 500 $\mu\text{g}/\text{m}^2/\text{d}$.

On Days 1, 3, and 5, naxitamab was infused i.v. over approximately 30 minutes.

In Phase 1, cycles were repeated at approximately 2- to 4-week intervals through Cycle 4, and subjects who completed 4 cycles of treatment without complication or disease progression had the option of continuing treatment for up to 24 months from their first dose of naxitamab. According to protocol, Phase 1 dose escalation ranged from 0.9 mg/kg per cycle to 10.8 mg/kg per cycle; however, dose escalation stopped at 9.6 mg/kg per cycle.

In Phase 2, cycles were repeated monthly through 5 cycles, and Group 1 and Group 3 subjects had the option of continuing treatment every 1 to 2 months for up to 24 months from trial enrollment or until they had received 5 cycles after a major response (CR or PR) was achieved, whichever came first. In Phase 2, the selected total dose per cycle was 9.0 mg/kg (3.0 mg/kg per infusion). See Section 6.2.2.1 for details.

Dose Modification, Dose Discontinuation

For adverse events (AEs) suspected to be related to naxitamab, management guidance and dose modifications were provided in the protocol. In the dose-escalation phase, Phase 1, subjects came off trial if they had a dose-limiting toxicity during the first cycle. In Phase 2, subjects were discontinued from naxitamab if their ADA titers exceeded a cutoff limit (>1300 U/mL), but could resume treatment if their ADA titer dropped below the cutoff limit. Investigators could discontinue trial drug for AEs associated with trial drug, including unacceptable toxicity or exacerbation of underlying disease.

Administrative Structure

Trial oversight was managed as follows:

- Memorial Sloan Kettering Cancer Center (MSK) served as the sponsor of the trial and was responsible for clinical trial management and data monitoring.
- Y-mAbs contracted clinical research associates who were independent of the trial to conduct on-site and remote data monitoring for the data used in the BLA.
- Y-mAbs commissioned the development of an electronic data capture system, and data entry support, data management oversight, and statistical analyses were performed by a contract research organization (CRO).

All laboratory assessments, including PK and ADA assessments, were conducted by MSK laboratories.

{DANYELZA, naxitamab-gqgk}

In addition, independent efficacy assessments were contracted by Y-mAbs: blinded, external, independent reviews of medical images and of pathology slides were conducted by board-certified radiologists and board-certified pathologists, respectively.

Procedures and schedule

Bilateral bone marrow aspirates and biopsies and imaging (CT, MRI, MIBG scan, and/or PET) for response evaluation were performed before treatment, during treatment before Cycle 3, and after Cycle 5 (Phase 1), and approximately every 3 months during Phase 2 and during follow-up. Complete history, physical exam, blood pressure, hematology, biochemistry, liver and kidney laboratory tests, urinalysis (Phase 1 only), pregnancy test, echocardiography (Phase 1 only), and electrocardiogram (Phase 1 only) were conducted prior to treatment and where relevant during treatment and follow-up. Blood for ADA assessment was drawn before each treatment cycle. Adverse events were recorded continuously and up to 30 days after the last treatment or until the subject began a new treatment, whichever was earlier.

Trial Endpoints

The BLA is submitted for Accelerated Approval based on the surrogate endpoint of overall response rate (ORR), defined as the sum of partial (PR) and complete responses (CR), supported by duration of response (DoR), which is defined as the interval between first response and progressive disease. ORR is recognized as an acceptable endpoint supporting accelerated approval for single-arm trials, as discussed and agreed with the FDA during a pre-IND meeting.

The response to therapy for neuroblastoma was assessed by the International Neuroblastoma Response Criteria (INRC), according to the revised INRC updated in 2017.[15]

Statistical Analysis Plan and Amendments

The statistical analyses for the interim analysis were defined in the protocol. A standalone statistical analysis plan (SAP) was made. There is only one version of the SAP. The SAP was signed after the statistical analyses of efficacy had started. The principal features in the SAP followed the ones in the protocol. The SAP deviated from the protocol in the following key features:

- Additional data (e.g., demographics, baseline characteristics, safety, efficacy subgroups) and corresponding analyses, to provide and facilitate an overall interpretation of the results, were specified in the SAP.
- The per protocol set analyses were not included in the SAP.

The analyses performed followed the SAP.

Efficacy Analysis

In Phase 2, subjects were enrolled into one of three subject groups described as follows:

- Group 1: Subjects with primary refractory disease (no prior relapse, but incomplete response to treatment) in bone and/or bone marrow, as documented by histology and or ¹²³I-MIBG scan.
- Group 2: Subjects in second CR or very good partial response and risk for another relapse. The VGPR criterium was removed from Group 2 enrollment criteria with Amendment 20.
- Group 3: Subjects with secondary refractory disease (prior relapse and incomplete response to retrieval therapy) in bone and/or bone marrow as documented by histology and/or ¹²³I-MIBG. (Note: hereafter this will be referred to as incomplete response to salvage treatment.)

Subjects from Group 2 had no tumor at baseline, therefore, this subject population is not part of the efficacy population but only contributes to the safety population.

The two efficacy analysis groups are the FAS (full analysis set) and PAS (primary analysis set). Both groups enrolled subjects with baseline disease defined in Groups 1 and 3 (primary refractory disease and incomplete response to salvage therapy, had evaluable disease at baseline, and began at least one infusion of naxitamab). The PAS was restricted to enrollments treated with greater than or equal to 3.0 mg/kg per infusion (cycle total of greater than or equal to 9.0 mg/kg), completing at least one cycle of naxitamab, irrespective of trial phase. The SAF (safety analysis set) was for the safety analysis and included all subjects that began an infusion of naxitamab.

Subgroup analyses based on relevant demographic and prognostic factors for efficacy evaluation were prespecified in the SAP.

Primary efficacy endpoint

The primary efficacy endpoint for the interim analysis of the pivotal Trial 12-230 was the ORR calculated along with a 95% confidence interval using the Clopper-Pearson exact methodology. As agreed at the pre-IND meeting with FDA, effectiveness was concluded if the lower limit of the exact 95% confidence interval was above 20%.

Secondary efficacy endpoint

The duration of response (DoR) was estimated using Kaplan-Meier methods and presented in a Kaplan-Meier plot. DoR was censored at the date of last disease assessment in subjects who did

{DANYELZA, naxitamab-gqgk}

not experience PD. As a conservative sensitivity analysis, DoR was also analyzed with descriptive summary statistics in which the subjects were considered to have progressed at last disease assessment.

Lack of evaluable disease at baseline

In line with International Council for Harmonisation E9 guidance (Section 5.2.1), subjects who lacked evaluable disease at baseline, as determined by the independent reviewers, were excluded from the efficacy analysis sets. All subjects in the Trial 12-230 Primary Analysis Set [PAS] had a completed baseline response assessment.

Safety Analysis

Safety analyses are defined and presented in Section 8.2.

PK Analysis

PK analysis is defined and presented in Section 6.2.1.

Protocol Amendments

The trial protocol was amended 22 times during the trial. None of the implemented changes impacted the integrity of the trial or the interpretation of the results. Key features of key amendments are summarized in the table below.

Amendment Number	Effective Date	Change
3	28 May 2013	- Increased the total number of cycles allowed per subject to 8 cycles, and after Cycle 4, the dose could be increased to the highest dose tested with completed DLT assessment. - A break between cycles after Cycle 4 of up to approximately 2 months was allowed.
5	21 Oct 2013	Introduced that subjects can continue up to 24 months on naxitamab.
8	13 Nov 2014	- Changed the DLT definition for laboratory liver enzyme elevations so that those that return to Grade 2 or lower within 14 days are not considered a DLT. - Increased the highest dose to be tested to 2.6 mg/kg. - Subjects with recurrent disease that can be completely eradicated without systemic therapy can stay in the trial.
10	06 Apr 2015	- Clarified the inclusion criteria regarding the period to be off chemotherapy or immunotherapy before starting naxitamab. - Dosage increase allowed at Cycle 3. - Increased the highest dose to be tested to 3.0 mg/kg. - After Cycle 2, only Grade 2 unexpected related AEs will be recorded.

{DANYELZA, naxitamab-gqgk}

Amendment Number	Effective Date	Change
12	08 Mar 2016	• Increase the highest dose to be tested to 3.6 mg/kg.
13	31 May 2016	• Added the Phase 2 portion of the trial.
14	25 Aug 2016	• Allowed subjects in Phase 2, to receive the three naxitamab doses over up to 10 days.
16	03 Feb 2017	• Subjects who paused naxitamab treatment due to ADA may receive local radiation therapy. • Changed to follow subject for 5 years after the first dose of naxitamab, and included additional blood draws. • Added that, for AEs, subjects will be followed for 30 days after last dose of naxitamab or start of new treatment, whichever is earliest.
19	05 Sep 2018	• Length of exposure to naxitamab was revised to 24 months or 5 cycles after a major response (CR or PR). • Revised the disease response criteria to remove the VGPR level and added ¹²³I-MIBG findings to the criteria.
20	16 Jan 2019	• Removed the level of VGPR from Group 2 enrollment criteria.
22	01 May 2019	• Added the interim analysis objectives and statistical analysis to the protocol.

The FDA's Assessment:

FDA generally agrees with the description of the trial provided by the Applicant with the exception of the definition of the efficacy population. FDA modified the proposed efficacy population to exclude additional patients based on the dose of naxitamab received, presence of progressive disease at baseline, radiation exposure to target lesions, lack of evaluable disease on central review, and timing of baseline disease assessment relative to completion of prior systemic therapy. Also, although the trial permitted patients to enroll multiple times in different cohorts, FDA considered only the first enrollment by each patient. The efficacy population as determined by FDA consisted of 38 unique patients, compared to 43 unique patients and 45 total enrollments in the Applicant's analysis.

FDA deemed it appropriate to revise the Applicant's definition of the efficacy population to include patients with baseline evaluable disease who initiated at least one infusion of naxitamab (as opposed to having completed at least one cycle) and received greater than or equal to 3.0 mg/kg per infusion. Two patients in the FDA efficacy analysis set received 3.2 mg/kg per infusion. For patients who enrolled in Study 12-230 more than once and received naxitamab dosages within this range during each enrollment, data

{DANYELZA, naxitamab-gqgk}

from the first enrollment was used rather than including response data from multiple enrollments for a given patient.

FDA notes that patients with progressive disease at the time of enrollment in the study (patients (b) (6) and (b) (6)) were excluded from the Applicant's efficacy population, consistent with the eligibility criteria for Trial 201 as described in Section 8.1.3. Upon further review of the patients included in the efficacy population, FDA noted that several patients had received radiation to target lesions, and in some cases to the only sites of evaluable disease. Patients enrolled in Trial 12-230 were permitted to receive radiation as medically necessary as determined by the investigator and these patients had no disease evaluable for response determination; therefore FDA excluded these patients from the efficacy population to permit a more accurate assessment of the efficacy of naxitamab. This resulted in an efficacy population of 38 unique patients, compared to 43 unique patients and 45 enrollments in the Applicant's analysis.

Table 8-1: Patients Excluded from 12-230 Efficacy Population due to Receipt of Radiation to Target Lesions

Patient ID	Comments
(b) (6)	This patient was reassessed by the Applicant as excluded from PAS since the patient had no MIBG at baseline available for central review. This patient was formerly classified as having a CR.
	Patient had PD prior to enrollment but was included in the Applicant's PAS. Received radiation to only site of MIBG-positive disease and had only bone disease.
	Per Applicant, had PD at study entry but included in the PAS. Received radiation and surgery to only evaluable site on study.
	Received radiation to only site of evaluable disease. Radiation was received approximately 6 months prior to enrollment in 12-230 and central radiology reviewers had discrepant reads of whether there was baseline MIBG positivity at that site. Best overall response was listed as a CR.

Several patients were excluded from the Applicant's analysis and from FDA's analysis given a lack of evaluable disease on central review. These patients were (b) (6), and

{DANYELZA, naxitamab-gqgk}

(b) (6). One additional patient (b) (6) was excluded based on timing of baseline disease assessment relative to receipt of prior systemic therapy, described below (Table 8-6).

FDA notes that disease evaluations in Trial 12-230 (including bone marrow evaluations and imaging) occurred post-Cycle 1, 4 and then every 3 months.

8.1.2. Trial Results

Compliance with Good Clinical Practices

The Applicant's Position:

The trial was conducted in accordance with the protocol, applicable regulatory requirements, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and with the Declaration of Helsinki (1989). The investigator conducted all aspects of this trial in accordance with all national, state, and local laws of the applicable regulatory agencies.

Before protocol-specified procedures were carried out, consenting professionals explained full details of the protocol and trial procedures as well as the risks involved to participants before their inclusion in the trial. Participants were also informed that they were free to withdraw from the trial at any time. All participants signed an IRB/PB-approved consent form indicating their consent to participate. This consent form met the requirements of the Code of Federal Regulations and the IRB/PB of this center.

The FDA's Assessment:

FDA has no additional comments.

Financial Disclosure

The Applicant's Position:

Refer to Section 19.2.

The FDA's Assessment:

Financial disclosures were provided by the Applicant and are summarized in Section 19.2.

{DANYELZA, naxitamab-gqgk}

Patient DispositionThe Applicant's Position:

FDA deleted this section based on revision of the efficacy population after discussion with the Applicant.

The FDA's Assessment:

The updated Disposition Table is shown in Table 8-3.

Table 8-2 Summary of Enrollment and Disposition, Trial 12-230

	Primary Efficacy Population (N=38) n (%)
Enrollments	38 (100.0)
Enrollments in Safety Analysis Set	38 (100.0)
Enrollments in Primary Analysis Set	38 (100.0)
Enrollments who Completed Study	11 (29)
Reasons for Off-Study	
Adverse Event	0
Excessive Toxicity	0
Progressive Disease	15 (39)
Received Prohibited Therapy	0
Withdrawal by Subject	1 (2.6)
At PI's Discretion	2 (5)
HAHA+	2 (5)
Receive Alternative Treatment or Enroll in Other Studies*	7 (18)

{DANYELZA, naxitamab-gqgk}

Protocol Violations/Deviations

The Applicant's Position:

Most protocol deviations were minor and concerned missed assessments, assessments out of window, and issues that were included in later protocol amendments (e.g., naxitamab dosing past that allowed by the protocol at the time, providing informed consent by phone for potential subjects with travel issues).

Nineteen subjects had at least one protocol deviation that was considered major. The type of major deviations fell into three types: informed consent, safety, and trial medication administration. Events reported as major protocol deviations included the following:

- Delays in reporting serious adverse events (SAEs) to the IRB (6 subjects)
- Blood draws for pretreatment assessment before signing consent (1 subject)
- Signature page of the consent having the incorrect amendment number (3 subjects)
- Trial medication administration issues that included the following:
 - Period between GM-CSF administration and start of naxitamab infusion (4 subjects)
 - Changes in GM-CSF administration days (2 subjects)
 - Missed or incorrect dose of GM-CSF (3 subjects)
 - Discontinuation of GM-CSF (2 subjects)
 - Change in dosing date for naxitamab (1 subject)
 - Multiple interruptions to naxitamab administration since the eCRF could only capture one (1 subject)

Four enrollments having major protocol deviations were part of the PAS group. No subjects were excluded from the PAS group due to major protocol deviations.

The FDA's Assessment:

FDA agrees with the description of protocol violations/deviations in 12-230 based on the information provided. The protocol violations/deviations described above are not expected to have a significant impact **on the validity of the safety or efficacy analyses for Trial 12-30.**

{DANYELZA, naxitamab-gqgk}

Table of Demographic Characteristics

The Applicant's Position

FDA deleted this section based on revision of the efficacy population after discussion with the Applicant.

The FDA's Assessment:

FDA requested a listing of the timing of receipt of all prior therapies and the specific therapies received in order to understand the definition of the efficacy population, which excluded patients with progressive disease. The patients with relapsed disease in the efficacy population in Trial 12-230 (n=21) had received a median of 2 lines of systemic therapy (range 1 to 4). The response to the most recent prior therapy was not uniformly reported.

FDA also asked for a comparison of the eligibility criteria for Trial 201, which was more specific, to the efficacy population in Trial 12-230. Of the patients included in FDA's efficacy analysis for Study 12-230, the following patient would not meet eligibility criteria for Study 201:

- Patient (b) (6): Patient would likely violate eligibility criterion requiring initiation of GM-CSF within 2 months of diagnosis of relapse, though the exact date of relapse was not recorded.

The remaining patients included in the efficacy population for Trial 12-230 meet the eligibility criteria for Trial 201.

FDA requested additional, detailed information regarding prior therapy and the timing of receipt of such therapy received by patients included in the efficacy population in order to better characterize the study population and any potential impact on the efficacy evaluation. The Applicant provided a detailed listing of therapies received, the response to such therapies as available, and the timing with respect to enrollment on Trial 12-230. Table 8-6 provides a listing of patients who demonstrated a partial or complete response to naxitamab and had a baseline scan and disease assessment < 4 weeks from the time of completion of systemic therapy. Patient (b) (6) was excluded from the efficacy population of the trial due to the receipt of systemic therapy up until the time of baseline disease assessment (i.e., this patient received their last dose of systemic therapy on the same day baseline imaging was obtained). Refer to the description of a sensitivity analysis performed by FDA with respect to the interval

{DANYELZA, naxitamab-gqgk}

between prior systemic therapy and baseline disease assessment in the description of the results of the primary endpoint.

Table 8-3: Responding Patients with Baseline Disease Assessments Less than Four Weeks from Prior Systemic Therapy in Trial 12-230

Subject ID	Disease Status	Last systemic therapy prior to enrollment on Study 12-230	Response to therapy, if available	Duration from end of systemic therapy to baseline disease assessment	Response/ Duration of Response to Naxitamab
(b) (6)	Incomplete response to salvage therapy	ASCT and cyclophosphamide, donor NK cells, hu3F8 and IL2 (MSK protocol 15-272)	'secondary refractory,' per site but response not provided (originally stated as CR, site confirmed patient secondary refractory, had MIBG avid disease)	3.6 weeks	PR, 8.14 weeks
(b) (6)	Incomplete response to salvage therapy	temozolomide and irinotecan (1.5 months duration)	Not provided	0 weeks	PR, 26.4 weeks
(b) (6)	Incomplete response to	Four cycles of chemotherapy with	Not provided	1.9 weeks	CR, 12 weeks

{DANYELZA, naxitamab-gqgk}

Subject ID	Disease Status	Last systemic therapy prior to enrollment on Study 12-230	Response to therapy, if available	Duration from end of systemic therapy to baseline disease assessment	Response/ Duration of Response to Naxitamab
	salvage therapy	last cycle of carboplatin, irinotecan, temozolomide			
(b) (6)	Primary refractory	Cyclophosphamide, topotecan, vincristine	Not provided	2.9 weeks	CR, 13.4 weeks
(b) (6)	Primary refractory	Cyclophosphamide, topotecan, vincristine	Not provided	2.6 weeks	CR, 23 weeks
(b) (6)	Primary refractory	"MSK high dose" cyclophosphamide, topotecan, vincristine	Not provided	2.1 weeks	CR, 31 weeks
(b) (6)	Primary refractory	Cyclophosphamide, doxorubicin, vincristine (ANBL 0532)	Stable disease	2.9 weeks	PR, 21.1 weeks
(b) (6)	Primary refractory	Cyclophosphamide, topotecan, vincristine	Not provided	2.9 weeks	CR, 23 weeks
(b) (6)	Primary refractory	Cyclophosphamide, doxorubicin, vincristine (ANBL 0532)	Not provided	1.6 weeks	CR, 31 weeks

{DANYELZA, naxitamab-gqgk}

Subject ID	Disease Status	Last systemic therapy prior to enrollment on Study 12-230	Response to therapy, if available	Duration from end of systemic therapy to baseline disease assessment	Response/ Duration of Response to Naxitamab
(b) (6)	Primary refractory	Cyclophosphamide, doxorubicin, vincristine (ANBL 0532)	Not provided	0.6 weeks	CR, 30.3 weeks
(b) (6)	Incomplete response to salvage therapy	Ifosamide, carboplatin, etoposide "low dose"	Not provided	3.0 weeks	CR, 21 weeks

Source: Primary review, Applicant response to FDA Information Request

The updated Baseline Disease Characteristic Table is shown below:

Table 8-4: Demographics and Baseline Characteristics of Primary Efficacy Population (N = 38), Trial 12-230

Demographics and Baseline Characteristics	Primary Efficacy Population (N = 38)
Sex, n (%)	
Female	19 (50)
Male	19 (50)
Age in years, median (range)	5.0 (2.0, 23.0)*
Race, n (%)	
White	28 (74)
Asian / Far East / Indian Subcontinent	3 (8)
Black / African American	2 (5)
Native American/American Indian/Alaska Native	2 (5)
Other	1 (3)
Refused to Answer	2 (5)
Ethnicity, n (%)	

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

{DANYELZA, naxitamab-gqgk}

Demographics and Baseline Characteristics	Primary Efficacy Population (N = 38)
Sex, n (%)	
Hispanic	1 (3)
Not Hispanic	36 (95)
Unknown	1 (3)
MYCN Status at Diagnosis, n (%)	
Amplification	6 (16)
Gain	1 (3)
Neither Gain nor Amplification	27 (71)
Not Reported	4 (11)
Disease Stage at Diagnosis, n (%)	
Stage 3	1 (3)
Stage 4	36 (95)
Not Reported	1 (3)
Disease Status, n (%)	
Incomplete Response to Salvage Therapy	21 (55)
Primary Refractory	17 (45)
Disease Involvement, n (%)	
Bone Only	19 (50)
Bone Marrow Only	4 (11)
Both	15 (39)
Prior Anti-GD2 Treatment, n (%)	
No	16 (42)
Yes	22 (58)
Prior Stem Cell Transplant, n (%)	
No	22 (58)
Yes	16 (42)
Prior Chemotherapy, n (%)	
Yes	38 (100)
Prior Radiation, n (%)	
No	20 (53)
Yes	18 (47)
Prior Surgery, n (%)	
Yes	38 (100)

Note: *One patient is greater than or equal to age 18;

Source: FDA reviewer-generated table using data submitted for Applicant for Trial 12-230 (ADSL, ADSL2)

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

{DANYELZA, naxitamab-gqgk}

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

All investigational products were prepared and administered in-clinic. Naxitamab compliance was calculated as the difference between the calculated planned dose (last recorded predose body weight x dose level in mg/kg) and the actual dose recorded in the subject CRFs. Calculated compliance for the first cycle averaged 100.1% (± 2.92 with a median of 99.9%). Over 25% of the infusions were within $\pm 1\%$ of the calculated dose, with 80.8% of the infusions being within $\pm 5\%$ of the calculated dose and 96.0% of the infusion within $\pm 10\%$. Individual compliance calculations ranged from 124.7% to 25.8%.

Concomitant Medications

Concomitant systemic therapy for neuroblastoma was not allowed during the trial.

However, subjects who developed an ADA titer greater than or equal to 1300 U/mL and therefore, could not have timely treatments with naxitamab and GM-CSF were eligible to receive low-dose maintenance regimens such as irinotecan alone, temozolomide alone, irinotecan-temozolomide, or cyclophosphamide-topotecan. They could also be treated with anti-ADA agents such as rituximab and cyclophosphamide. Naxitamab and GM-CSF treatments could be resumed when the ADA titer fell below 1300 U/mL.

Pretreatment was allowed before naxitamab infusions with analgesics for pain (e.g., hydromorphone) and antihistamines (e.g., diphenhydramine or hydroxyzine).

No major protocol deviations due to the use of prohibited concomitant medications were reported.

Rescue medication

Surgical and radiotherapy was allowed for subjects whose neuroblastoma progressed. It was at the discretion of the investigator to decide if naxitamab treatment was to be continued.

The FDA's Assessment:

Additional information was requested regarding the use of chemotherapy for patients

{DANYELZA, naxitamab-gqgk}

who developed an ADA titer greater than or equal to 1300 U/mL on treatment. Six of 43 patients in the efficacy population had a positive ADA test on treatment and one received systemic therapy on study. This patient received rituximab (with celecoxib premedication) and cyclophosphamide and did not demonstrate an objective response. Therefore, the reviewer is not concerned that receipt of chemotherapy administered to patients who had a positive ADA contributed to any objective responses observed in this trial based on the information provided.

FDA notes that radiation was permitted in Trial 12-230 as clinically indicated after cycle 1. Some patients received radiation to sites of disease prior to the onset of an objective response; patients included in the efficacy analysis who received radiation are listed in Table 8-7 below. Based on receipt of radiation to some target lesions, the best overall response for some patients were reassessed as a PR compared to the prior assessment of CR. Areas of overlap between sites of target lesions and sites of radiation therapy are highlighted in yellow below. Radiation was administered soon after treatment was initiated in all cases. As summarized in the table, based on the information available, this reviewer considers that the observed objective responses cannot be attributed to administration of radiation in these patients; however, administration of radiation may have prevented progression in the irradiated lesions, which would have resulted in an overall response by INRC of disease progression. Concomitant administration of radiation must be considered when interpreting the efficacy results of the trial.

Table 8-5: Patients in Trial 12-230 Efficacy Population who Received Radiation Prior to Onset of an Objective Response

Patient ID	Naxitamab Treatment Dates	Best Response	Site of Target Lesions	Site of Radiation Therapy	Comments
(b) (6)	(b) (6)	CR	Bone marrow disease only	Lt Neck, Chest and Abdomen (On treatment: (b) (6))	No area of overlap between target lesions and sites of radiation
(b) (6)	(b) (6)	CR	Bone and bone marrow	Abdomen (On treatment: (b) (6))	No area of overlap between target lesions and sites of radiation

{DANYELZA, naxitamab-gqgk}

Patient ID	Naxitamab Treatment Dates	Best Response	Site of Target Lesions	Site of Radiation Therapy	Comments
			MIBG positive: Femur, head, lower legs, lumbar spine, pelvis, upper arms		<i>Reviewer note: Upon review, this patient did not have a confirmed response of CR, and was therefore considered a non- responder in FDA's efficacy analysis.</i>
(b) (6)	(b) (6)	CR	Bone and Bone Marrow Disease MIBG positive: Femur*	Abdomen, R femur* (On treatment: (b) (6))	Overlap between MIBG positive site and site of radiation. Assessed as bone marrow-only with CR. <i>FDA agrees with the reassessment as bone marrow only given radiation of only MIBG positive site.</i>
(b) (6)	(b) (6)	CR	Bone and Bone Marrow Disease MIBG positive: femur, head,* lower arms, lower legs, lumbar spine, upper arms, pelvis	Abdomen, outer calvarium, R calvarium, L calvarium* (On treatment: (b) (6))	Also has bone marrow disease and sites that were not irradiated. <i>FDA considers that there were bony areas outside of the radiation area, which would not be expected to respond to local radiation delivered elsewhere, and the response of</i>

{DANYELZA, naxitamab-gqgk}

Patient ID	Naxitamab Treatment Dates	Best Response	Site of Target Lesions	Site of Radiation Therapy	Comments
					<i>CR is appropriate despite radiation administered.</i>
(b) (6)	(b) (6)	PR	Bone Disease MIBG positive: head, lumbar spine, thoracic spine	Abdomen and L neck; Abdomen CD (On treatment: (b) (6))	Per Applicant there was no overlap in areas of target lesions and radiation received. Patient has sites that were not irradiated.
(b) (6)	(b) (6)	CR	Bone and Bone Marrow Disease MIBG positive: femur, lower legs, lumbar spine, thoracic spine, upper arms	Pancreatic bed and nodes (On treatment: (b) (6))	Per Applicant there was no overlap in areas of target lesions and radiation received.
(b) (6)	(b) (6)	CR	Bone and Bone Marrow Disease MIBG positive: head*, pelvis	Abdomen, R temporal skull, R frontal skull* (On treatment: (b) (6))	Skull lesions which were MIBG positive were irradiated. Patient also has bone marrow disease and sites that were not irradiated. FDA considers the assessment of CR reasonable.
(b) (6)	(b) (6)	CR	Bone and Bone Marrow Disease	L humerus, outer skull, L/R skull*, orbit maxilla and L parietal boost	Also has bone marrow disease and sites that were not irradiated (R arm).

{DANYELZA, naxitamab-gqgk}

Patient ID	Naxitamab Treatment Dates	Best Response	Site of Target Lesions	Site of Radiation Therapy	Comments
			MIBG head, upper arms* <i>Reviewer infers bilateral arms</i>	(On treatment: (b) (6))	Applicant assessed as having only bone marrow involvement with a CR, but given non-radiated sites FDA considers this patient as having bone and bone marrow disease.

*Areas of overlap between target lesions and sites receiving radiotherapy are highlighted in yellow.

Source: Primary review, response to FDA information requests

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

Overall Response Rate (ORR)

FDA deleted this section based on revision of the efficacy population after discussion with the Applicant.

The FDA's Assessment: FDA does not agree with the primary efficacy analyses results. Treatment with naxitamab in combination with GM-CSF lead to an ORR of 34% (95% CI: 20, 51). The primary efficacy results based on 38 individual patients is shown in the following table:

Table 8-6: Overall Response Rate in the Primary Efficacy Population, Trial 12-230

Best Overall Response by BICR	Primary Efficacy Population (N = 38)
Overall response rate, n (%)	13 (34)
Clopper-Pearson 95% CI	(20, 51)
Complete Response, n (%)	10 (26)
Partial Response, n (%)	3 (8)

Source: FDA reviewer-generated table using data submitted by Applicant for Trial 12-230(ADRESP) There were several review issues in FDA's evaluation of the primary endpoint, including the method for determining the overall response by INRC, the method of handling soft tissue disease in the assessment according to the INRC, and the assessment and potential confounding of the efficacy results due to a short interval between prior systemic therapy and the baseline scan for Trial 201.

Review Issue: Assessment of Overall Response per INRC

Individual components of the responses used assess the response to naxitamab using the revised INRC (measurement of soft tissue lesions, bone marrow evaluations, and MIBG/FDG evaluations) were independently reviewed and the charters for the independent review of the components of response was included in the BLA; however, the overall assessment of response based on the INRC was made by the Applicant based on the independently reviewed components. During the review, FDA requested detailed listings including detailed information about the inclusion of soft tissue lesions in the overall assessment of response and evaluated the overall response determination per INRC made by the Applicant.

Reviewer assessment: The reviewer considered that the overall response per INRC as determined by the Applicant was acceptable in the context of this trial.

Review Issue: Assessment of Soft Tissue Lesions in Overall Response Assessment

The Applicant provided an overview of response assessment in soft tissue lesions. The Applicant stated that exclusion of patients with soft tissue disease at baseline was at the investigator's discretion and that patients with soft tissue disease expected to be scar tissue were permitted to enroll. Baseline soft tissue disease was followed by CT/MRI and evaluated independently, but the external radiology review was not asked to assess whether disease represented active tumor,

{DANYELZA, naxitamab-gqgk}

and MIBG/PET results were not considered in the assessment of soft tissue disease based on the independent review charter.

Reviewer note: The revised INRC assessment of soft tissue disease incorporates use of MIBG/FDG for assessment of response and defining target lesions.

Local radiotherapy for soft tissue disease was permitted during the trial. Although the appearance of new soft tissue lesions, or progression in existing soft tissue disease, were incorporated in the overall assessment per INRC, responses in baseline soft tissue lesions were not incorporated into the overall response assessment by INRC because they were not considered active disease and therefore were not considered 'target lesions.' Administration of local radiation to sites of soft tissue disease is not expected to contribute to the responses observed given that these sites were not considered target lesions and only progression (and not responses) in soft tissue would result in a change in overall assessment of response.

Below is a summary of each patient with soft tissue disease at baseline or during the trial, and an assessment of how this impacted FDA's assessment of overall response.

- (b) (6): there was a soft tissue lesion (STL) considered not evaluable at baseline, and a new STL was detected on (b) (6) and based on independent imaging and pathology review PD in bone or bone marrow on the same date. No consequences for overall best response.
- (b) (6): STL at baseline; 19.1 mm shrinking to 12.4 mm. Based on independent imaging and pathology review the patient had CR in bone and bone marrow. No consequences for overall best response.

Reviewer note: The patient is noted to have a CR according to independent response listings. The sponsor provided information to support their assertion that the soft tissue lesion was not considered active tumor, namely that the area was not MIBG-avid at baseline and was interpreted by independent imaging as "liver lesion probably post treatment."

This patient received radiation to abdominal disease and bony disease in the calvarium soon after enrollment on trial. The patient had bony disease elsewhere (femur). The sponsor states that the soft tissue disease was assessed as scar tissue and response in the soft tissue disease was not included in the assessment of response.

{DANYELZA, naxitamab-gqgk}

- (b) (6): No STL at baseline, new STL on (b) (6) based on independent imaging and pathology review and a CR in bone and bone marrow was observed on the same date. Based on these responses, the best overall response per INRC was determined to be a PD in (b) (6) based on new soft tissue lesion.
Reviewer note: The patient received radiation to the primary tumor bed (abdomen), skull, and supraclavicular lymph nodes shortly after enrolling on study. This is not described in Table 8-6 since an objective response (PR or CR) was not demonstrated in this patient.
- (b) (6): STL at baseline. No further STLs recorded. No consequences for overall response.
Reviewer note: This patient had thoracic paraspinal radiation approximately one month after initiating study therapy. The soft tissue disease was not considered active disease and was not included in the response assessment; this patient's best response was PD.
- (b) (6): STL at baseline, new STL (b) (6) where SD was assessed in bone and bone marrow. Accounting for the new STL, the overall best response for this patient changes from SD to PD. No consequence for DoR since the patient did not have CR or PR.
Reviewer note: The patient received radiation in (b) (6) to base of skull, bilateral neck, and thorax. The patient continued to receive naxitamab until (b) (6). The reviewer agrees that the patient did not achieve an objective response and thus there is no impact on ORR or DoR.
- (b) (6): No STL at baseline, new STL on (b) (6) and based on independent imaging and pathology review PD in bone or bone marrow on the same date. No consequences for overall best response.
Reviewer note: As indicated in Table 8-6, this patient had radiation to the abdomen shortly after enrollment. Per the sponsor, patient did not have measurable soft tissue disease per blinded review. In addition, this patient did not have a confirmed response and was not considered a responder in the FDA analysis.
- (b) (6): This patient had radiation to the left neck, chest and abdomen shortly after initiation of treatment with naxitamab; per the sponsor, radiation was to post-surgical sites. Reported response is CR, and FDA agrees, considering bone marrow as the only target lesion.
- (b) (6): This patient received radiation to the abdomen (soft tissue) and femur shortly after initiation of treatment with naxitamab. Reported response is CR and FDA agrees, considering only bone marrow as the target lesion.

{DANYELZA, naxitamab-gqgk}

- (b) (6): This patient received radiation to the abdomen (soft tissue) shortly after initiation of treatment with naxitamab. Reported response is PR and FDA agrees, considering bone and bone marrow as target lesions.
Reviewer note: The patient has a reported PR. At 6 months post onset of response, the patient demonstrated a CR in bone, but there was no bone marrow assessment (overall response: NE). Given the incomplete assessment at 6 months, the patient's proven duration of response was conservatively considered to be 3 months by FDA, not 6 months as reported by the Applicant.
- (b) (6): This patient received radiation to the pancreatic bed and nodes (soft tissue) shortly after initiation of treatment with naxitamab. Reported response is CR and FDA agrees, considering bone and bone marrow as target lesions.
- (b) (6): This patient received radiation to the abdomen (soft tissue) shortly after initiation of treatment with naxitamab. Reported response is PR, and FDA agrees considering bone marrow only.

The reviewer considers that radiation is not expected to contribute to the overall responses observed. Ultimately, based on the information provided, it appears the approach of not including soft tissue responses in the INRC assessment, considering that these lesions are not assessed as active tumor (i.e., were not considered target lesions), is acceptable.

Review Issue: Duration between Prior Therapy and Baseline Disease Assessment

FDA considered whether the short time from completion of systemic therapy until the baseline disease assessment could confound the assessment of response to naxitamab. In practice, the urgency to enroll patients, particularly with primary refractory disease who may have demonstrated stable disease, minor response or partial response to prior intensive chemotherapy, onto a clinical trial may render a standard washout period from prior therapy (i.e., at least 4 weeks prior to baseline disease assessment) challenging. Since patients with progressive disease were excluded from the trial, patients with relapsed disease were treated first with other therapy (typically chemotherapy or chemotherapy and immunotherapy) prior to enrollment, thus the concern that the effect of prior therapy is not reflected in the baseline disease assessment (and thus that responses observed in the trial cannot wholly be attributed to naxitamab) is greater in this population.

FDA performed a sensitivity analysis excluding patients (non-responders and responders) from the efficacy population who had a baseline scan < 2.5 weeks from the time of completion of systemic therapy. In Trial 12-230, this criterion applied to 5 responders and 4 non-responders,

{DANYELZA, naxitamab-gqgk}

resulting in 9 responders among 30 patients (ORR 30%), slightly lower than the ORR without the sensitivity analysis.

Because this sensitivity analysis excluded responding patients with durable complete responses which the review team did not consider reasonably attributable to prior therapy, FDA decided to only exclude those patients who received systemic therapy up until the time of the baseline scan (i.e., those patients with a time from systemic therapy to baseline scan of zero weeks) from the efficacy population; this applied to one patient in the efficacy population, patient (b) (6).

Subgroup analyses

The Applicant's Position:

Subgroup analyses are summarized in Section 8.1.8. Although these supporting subgroup analyses were not powered to show statistical significance, they consistently demonstrated benefit of naxitamab treatment across relevant subgroups.

The FDA's Assessment: FDA in addition conducted subgroup analyses by demographic characteristics, as shown in the following table.

Table 8-7: Summary of ORR Subgroup Analyses by Demographic Characteristics, Trial 12-230

	N	ORR, % (95% CI)
Sex		
Female	19	37 (16, 62)
Male	19	32 (13, 57)
Age		
< 6 years	20	40 (19, 64)
6 – 12 years	13	38 (14, 68)
≥ 12 years	5	0 (0, 52)
Race, n (%)		
White	28	25 (11, 45)
Asian	3	67 (9, 99)
Other	7	57 (18, 90)

Source: FDA reviewer-generated table using data submitted by Applicant for Trial 12-230 (ADRESP) ;

FDA notes the response rate in patients with prior GD2-directed therapy (18%, 95 CI: 5%, 40%) is of particular clinical relevance given the availability and use of anti-GD2

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

{DANYELZA, naxitamab-gqgk}

antibodies in the treatment of patients with high risk neuroblastoma. Given the small sample size for this subgroup, results must be interpreted with caution. In addition, among the 22 patients who received anti-GD2 treatment prior to their first enrollment on Trial 12-230, 19 (86%) had relapsed disease and were more heavily pre-treated than the patients with primary refractory disease.

Table 8-9 presents the exploratory subgroup analysis of the response rate by both prior anti-GD2 antibody exposure and disease status. Although the number of patients in the subgroups in this analysis are extremely small, results of this analysis appear to show that there is a trend toward a better response rate in patients with no prior anti-GD2 exposure regardless of whether they had relapsed or primary refractory disease.

Table 8-8: Overall Response Rate Subgroups by Anti-GD2 Exposure and Baseline Disease Status in Trial 12- 230

	Prior Anti-GD2	No prior anti-GD2
<i>Incomplete response to salvage therapy</i>		
N	19	2
ORR, % (95% CI)	21 (6, 46)	100 (16,100)
<i>Primary refractory</i>		
N	3	14
ORR, % (95% CI)	0 (0, 71)	50 (23,77)

Source: FDA reviewer-generated table using data submitted by Applicant for Trial 12-230 (ADRESP) ;

Data Quality and Integrity

The Applicant's Position:

The results from the performed data quality assurance procedures yielded no reason for concerns.

The FDA's Assessment:

FDA agrees that the data quality was sufficient to permit review of the application. However, the limitations in data collection (e.g. lack of disease assessments beyond the end of treatment) as well as the use of atypical variables, resulted in significant review issues. Numerous IRs were necessary in order for the review team to adequately

ascertain the quality and integrity of the data.

Efficacy Results – Secondary and other relevant endpoints

Duration of response (DoR)

The Applicant's Position:

FDA deleted this section based on revision of the efficacy population after discussion with the Applicant.

The FDA's Assessment: FDA in general agrees with sponsor's analyses and the median DOR was not reached. The results of analyses is summarized in Table 8-10.

Table 8-9: Summary of Duration of Response, Trial 12-230

	Responders (N = 13)
Duration of Response	
Median, months (95% CI)	NR (NE, NE)
Range, months	(1.9+, 7.1+)
Percent of responders with DOR $\geq$ 3 months	85%
Percent of responders with DOR $\geq$ 6 months	23%

+: censored; NR: Not reached; NE: Not estimable;

Source: FDA reviewer-generated table using data submitted by Applicant for Trial 12-230 (ADRESP) ;

Interpretation of duration of response is limited by the lack of systematic follow-up of responders after discontinuation of treatment with naxitamab. The protocol did not require continued assessments of response after end of treatment, patients may have been followed at another institution, and some received subsequent anti-cancer therapy prior to demonstration of progression. FDA inquired if a later data cut-off for evaluation of duration of response was available for a more mature characterization of DOR, but given the limitations in study assessments and data collection, additional data was not available. It is therefore uncertain whether these limitations have resulted in an underestimation of duration of response.

{DANYELZA, naxitamab-gqgk}

Dose/Dose Response

The Applicant's Position:

In an analysis of Trial 12-230 by dose level (≥ 3.0 mg/kg/infusion (45 enrollments (PAS)) vs < 3.0 mg/kg/infusion (15 enrollments)) the ORRs appeared similar between the two groups. However, importantly the CR rate was higher in the ≥ 3.0 mg/kg dose group compared to the < 3.0 mg dose group (31.1% vs 20.0%). Achieving a CR is of major clinical significance. Based on the information above, the dosing regimen of 9 mg/kg per cycle was determined to present the best balance between a manageable safety profile while ensuring effect of naxitamab treatment.

The FDA's Assessment:

FDA notes that the data presented regarding the efficacy of doses < 3.0 mg/kg/dose is limited and should be interpreted with caution.

Durability of Response

The Applicant's Position:

This is addressed under the secondary endpoint, Duration of Response, above.

The FDA's Assessment:

FDA has no further comments.

Persistence of Effect

The Applicant's Position:

This is addressed under the secondary endpoint, Duration of Response, above. No long-term efficacy data, with the exception of those presented in the preceding sections, are available at the time of this application.

The FDA's Assessment:

FDA agrees with the Applicant that data regarding the persistence of effect beyond discontinuation of naxitamab is not addressed in the Application.

{DANYELZA, naxitamab-gqgk}

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA has no further comments.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA has no further comments.

8.1.3. Trial 201

The Applicant's Description:

Trial Design

Trial 201 is an ongoing, multicenter, international, single-arm, nonrandomized, open-label, Phase 2 trial to evaluate the safety and efficacy of naxitamab administered with GM-CSF in high-risk neuroblastoma subjects with primary refractory disease or incomplete response to salvage treatment in bone and/or bone marrow. In contrast to Trial 12-230, subjects could only be enrolled once in Trial 201.

In Trial 201, subjects underwent the same naxitamab treatment cycles as described for Trial 12-230. Treatment cycles were repeated every 4 weeks (± 1 week) until CR or PR followed by five additional cycles every 4 weeks (± 1 week). Subsequent cycles could be repeated every

{DANYELZA, naxitamab-gqgk}

8 weeks (± 2 weeks) through 101 weeks from first infusion at the discretion of the investigator. After end of treatment (EOT), each subject will enter a long-term follow-up for 3 years in which they will be monitored at the referral site.

In agreement with the FDA, Trial 201 data were based on an interim analysis and provide support that the efficacy results obtained in Trial 12-230 are reproducible. However, the interim analysis was not statistically powered to demonstrate efficacy.

Trial Location

The trial is being carried out at three sites: Two sites in the United States (9 subjects) and one site in Spain, Europe (16 subjects).

Choice of Control Group

Since high-risk neuroblastoma is a rare disease, the trial is single-arm with no comparator.

Diagnostic Criteria

The trial enrolled subjects with neuroblastoma diagnosed by 1) histopathology of tumor biopsy or 2) bone marrow aspirate or biopsy indicative of neuroblastoma by histology plus high urine catecholamine levels or MYCN amplification or MIBG-avid lesion(s).

Key Inclusion/Exclusion Criteria

Enrollment was open to subjects older than 1 year of age with a diagnosis of neuroblastoma, as defined in the section on diagnostic criteria above. Subjects should have high-risk neuroblastoma with either primary refractory disease or incomplete response to salvage treatment, evaluable in bone and/or bone marrow; if disease was only present in bone, the subject should have evaluable disease outside the radiation areas for being eligible.

The subject should have acceptable hematological status and acceptable liver and kidney function as defined in the protocol.

Subjects were excluded for any systemic anticancer therapy, including chemotherapy or immunotherapy within 3 weeks before the first dose of GM-CSF. Subjects were also excluded for evaluable neuroblastoma outside bone and bone marrow sites.

High-risk neuroblastoma (NB) was defined as INRG [15, 16] MYCN-amplified any INRG stage of any age, or MYCN-nonamplified with INRG Stage M subjects, diagnosed at 18 months of age or older.

{DANYELZA, naxitamab-gqgk}

Primary refractory disease was defined as no relapse or PD, but incomplete metastatic response (SD, MR, PR defined by INRC) to treatment in bone and/or BM as documented either by histologic evidence of NB in bone or BM and/or abnormal ^{123}I -MIBG uptake in skeletal sites. In addition, at trial enrollment, subjects could not be more than 18 months from initiation of chemotherapy and must have received at least 4 cycles of standard induction chemotherapy for high-risk NB.

Incomplete response to salvage treatment was defined as relapse or PD, and incomplete response (SD, MR, PR, but not PD, defined by INRC) to salvage chemotherapy or MIBG therapy immediately before enrollment. Furthermore, it was restricted to lesions in bone and/or BM as documented either by histologic evidence of NB in bone or BM and/or abnormal ^{123}I -MIBG uptake in skeletal sites. In addition, a minimum of 2 months from last MIBG/PET-CT documented relapse or PD prior to enrollment was required.

Dose Selection

As in Trial 12-230, the dose level was 9.0 mg/kg per cycle administered on Days 1, 3, and 5 of each cycle (3.0 mg/kg per infusion) in the presence of s.c. GM-CSF (Days –4 through 5).

Trial Treatments, Treatment Assignment, and Blinding

Trial 201 is an open-label, single-arm trial.

As in Trial 12-230, each subject received naxitamab with GM-CSF over a 10-day period in a cycle. A cycle started with 5 days of GM-CSF administered s.c. at $250\text{ }\mu\text{g}/\text{m}^2/\text{d}$ before the start of naxitamab infusions (Day –4 to Day 0) (Figure 8-1). On Days 1 through 5, GM-CSF was administered s.c. at a dose of $500\text{ }\mu\text{g}/\text{m}^2/\text{d}$.

On Days 1, 3, and 5, naxitamab was infused i.v. over approximately 30 minutes.

Dose modification, dose discontinuation

For AEs suspected to be related to naxitamab, management guidance and dose modifications were provided in the protocol. Investigators could discontinue trial drug for adverse events considered related to the trial drug.

Administrative structure

Trial oversight was managed by Y-mAbs as the sponsor of the trial. The trial was monitored by a CRO contracted by Y-mAbs. Furthermore, data management oversight and statistical analyses were performed by a CRO.

{DANYELZA, naxitamab-gqgk}

All laboratory assessments, including PK and ADA assessments were conducted by an external independent laboratory contracted by Y-mAbs.

In addition, independent efficacy assessments were contracted by Y-mAbs: blinded, external independent reviews of medical images and of pathology slides were conducted by board certified radiologists and board certified pathologists, respectively.

Procedures and schedule

Imaging (by CT/MRI and ¹²³I-MIBG scans/FDG-PET or MIBG.SPECT/CT) and bone marrow pathology (bilateral bone marrow aspirates and bone marrow biopsies) for response evaluation was performed at screening within 4 weeks before treatment, during treatment before Cycle 3, and approximately every 3 months. Complete history, physical exam, blood pressure, hematology, biochemistry, pregnancy test, electrocardiogram, and blood for ADA and PK, were conducted prior to treatment and where relevant during treatment and follow-up. Adverse events were recorded continuously and up to 30 days after the last treatment.

Trial Endpoints

The primary efficacy endpoint for the interim analysis was the ORR based on independent, external, expert assessments, up to the interim data cutoff date. As for Trial 12-230, ORR was assessed according to the INRC. The secondary endpoint was DoR.

Statistical Analysis Plan and Amendments

A standalone SAP was made for the interim analysis performed to support the BLA. There is only one version of the SAP. The SAP was signed after the statistical analyses of efficacy had started. The principal features in the SAP followed the ones in the protocol. The SAP deviated from the protocol in the following features:

- The definitions of Cohorts 1 and 2 in the SAP were aligned with feedback from FDA and the subsequently amended protocol.
- Analyses of progression-free survival and overall survival were not included (data not yet sufficiently mature).
- The ADA-positive subgroup analyses in the clinical trial protocol were omitted: too few subjects (n=2) were ADA-positive for such analyses to be informative. Instead, subgroup analyses per relevant baseline disease status and disease compartments were introduced.

The analyses performed followed the SAP.

{DANYELZA, naxitamab-gqgk}

Efficacy analysis

The interim analyses provide results for the assessment of the interim primary endpoint, independently assessed ORR, and the secondary endpoint, DoR.

Two cohorts of subjects are enrolled in the trial:

- Cohort 1 includes subjects who are screened negative for ADA and with no preplanned radiotherapy for metastatic lesions.
- Cohort 2 includes subjects who are screened positive for ADA or with preplanned radiotherapy for metastatic lesions.

Primary and secondary interim efficacy analyses were performed on the full analysis set (FAS). The FAS consisted of 22 subjects in Cohort 1 who had evaluable disease at baseline, received at least one infusion of naxitamab and had at least one follow-up before the interim data cutoff date.

Cohort 1 was the only cohort used for primary and secondary efficacy analysis. Cohort 2 (includes one subject only) was included for exploratory efficacy and safety analyses only.

Protocol Amendments

The trial protocol was amended 5 times during the period covered by the trial report. None of the implemented changes impacted the integrity of the trial or the interpretation of the results. Key features of key amendments are summarized below:

Amendment Number	Effective Date	Change
1.0	Effective date 12 Apr 2018	• Specified that the primary endpoint “ORR during the naxitamab treatment period” will be centrally assessed according to INRC. • Added any systemic anticancer therapy within 3 weeks prior to the start of naxitamab to the exclusion criteria. • Updated the long-term follow-up period from 5 years to 3 years. • Updated definition of primary and secondary refractory disease to include disease in bone.
2.0	Effective date 30 Aug 2018	• Added the secondary objective “to evaluate the complete response to naxitamab and GM-CSF.” • Added the secondary objective “to evaluate the safety of naxitamab + GM-CSF in subjects with positive ADA at trial entry.” • Updated secondary endpoint for DoR to define patient response as CR or PR, and to add that data will be censored for ongoing responses. • Updated secondary endpoint for OS, to add that data will be censored at last known date alive.

{DANYELZA, naxitamab-gqgk}

Amendment Number	Effective Date	Change
		- Added secondary endpoint on intravenous opioid use during treatment cycles. - Added secondary endpoint on incidence of AEs and SAEs in subjects with positive ADA at inclusion. - Added the exclusion criteria, “prior treatment with naxitamab.” - Added the exclusion criteria, “Karnofsky/Lansky score <50%.” - Updated number of subjects planned to be enrolled to include definition of Cohort 1 subjects. - Updated schedule of bone marrow aspirates and biopsies.
3.0	Effective date 24 Sep 2018	Added exclusion criterion “history of anaphylactic reactions CTCAE Grade 4 related to prior GD2 antibody therapy” as part of an urgent safety measure effective immediately.
4.0	Effective date 18 Oct 2018	Added exclusion criteria, “history of anaphylactic reactions CTCAE Grade 4 related to prior GD2 antibody therapy.”
5.0	Effective date 07 Feb 2019	- Updated clinical management of selected naxitamab adverse reactions. - Updated premedications prior to naxitamab infusions.

The FDA’s Assessment:

FDA notes that the study population enrolled in Trial 201 as defined above represents a subset of patients with relapsed and refractory high-risk neuroblastoma. Patients with progressive disease at study entry were excluded according to the definition above; this definition has also been applied in the efficacy population for Trial 12-230. Patients with disease outside the bone or bone marrow were excluded per eligibility criteria; in Trial 12-230, patients in Phase II were required to have primary or secondary refractory disease in BM and/or abnormal 123I-MIBG uptake in osteomedullary sites.

FDA notes that while the description of Cohorts 1 and 2 above states that patients in Cohort 2 could have pre-planned radiation to metastatic sites, patients in Cohort 1 could also receive radiation to the primary site of disease provided they had not already received radiation to this site. Patients with primary refractory disease may have discontinued standard first line therapy for high risk neuroblastoma prior to receipt of radiation to the primary disease site.

Although the protocol excluded patients with evaluable disease outside of the bone or bone marrow, several patients had soft tissue lesions present at baseline (see discussion in Section 8.1.4).

{DANYELZA, naxitamab-gqgk}

FDA notes that in later versions of the study protocol, the definition of Cohorts 1 and 2 were revised such that patients with bone marrow only disease are included in Cohort 2. The description of Cohorts 1 and 2 provided above reflects the definition applied for the clinical study report and the FDA analyses; therefore, patients with disease confined to the bone marrow are included in this analysis.

Unlike the protocol for Trial 12-230, the protocol for Trial 201 provided extensive advice regarding pre-medication for naxitamab infusion. This was based on the increased frequency and severity of infusion reactions, including serious infusion reactions and anaphylaxis requiring urgent intervention observed in Trial 201 compared to Trial 12-230 (See Section 8.2.4 for discussion). This included (as of protocol version 8.0, dated February 7, 2019):

- Gabapentin, initiated starting on Day -4 before naxitamab infusion
- Opioids (oral preferred)
- Corticosteroids administered 30 minutes to 2 hours prior to infusion, given prior to the first dose and in the following situations:
 - At the first infusion in the following cycle if the subject had a Grade 3 bronchospasm/anaphylaxis at the first infusion of the last treatment cycle
 - At the next naxitamab infusion if the subject had a Grade 3 bronchospasm/anaphylaxis at the last infusion
 - At the investigator's discretion when infusion related reactions were not controlled by other pre-medications to the attending physician's satisfaction.
- Antipyretics
- Antihistamines
- H2 antagonists
- Antiemetics
- Anxiolytics (if applicable)

8.1.4. Trial Results

Compliance with Good Clinical Practices

The Applicant's Position:

The trial was conducted in accordance with the protocol, applicable regulatory requirements, Internal Council for Harmonisation (ICH) Good Clinical Practice (GCP), and

{DANYELZA, naxitamab-gqgk}

with the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Association in Helsinki, Finland, in 1964 and subsequent versions.

Before protocol-specified procedures were carried out, patient and legal representative received full details of the protocol and trial procedures, both verbally and written, before consent was given. Participants were also informed that they were free to withdraw from the trial at any time. All participants signed an IRB/IEC approved consent form indicating their consent to participate.

The FDA's Assessment:

FDA concurs and has no additional comments.

Financial Disclosure

The Applicant's Position:

Refer to Section 19.2

The FDA's Assessment:

FDA has no additional comments. See Section 19.2.

Patient Disposition

A total of 25 subjects enrolled in Trial 201 during the period covered by the interim trial report. At the time of data cutoff, 12 (48.0%) subjects were continuing in the trial, and 13 (52.0%) subjects had discontinued from the trial. Of these, 8 subjects withdrew due to progressive disease, 2 subjects due to an adverse event, 2 subjects completed the trial, and 1 subject met withdrawal criteria (see Table 8-7).

Table 8-10 Summary of Enrollment and Disposition, Trial 201 Safety Analysis Set

	Cohort 1 (N=24)	Cohort 2 (N=1)	Total (N=25)
Subjects exposed to naxitamab (Safety Analysis Set), n (%)	24 (100.0)	1 (100.0)	25 (100.0)
Subjects in the Full Analysis Set	22 (91.7)	1 (100.0)	23 (92.0)
Subjects discontinuing in the study, n (%)	13 (54.2)	0	13 (52.0)

{DANYELZA, naxitamab-gqgk}

	Cohort 1 (N=24)	Cohort 2 (N=1)	Total (N=25)
Reason for discontinuation from the trial ¹			
Adverse event, n (%)	2 (15.4)	0	2 (15.4)
Completed	2 (15.4)	0	2 (15.4)
Progressive disease, n (%)	8 (61.5)	0	8 (61.5)
Withdrawal criteria met, n (%)	1 (7.7)	0	1 (7.7)
Reason for discontinuation of study drug ²			
Adverse event	1 (25.0)	0	1 (25.0)
Progressive disease	3 (75.0)	0	3 (75.0)

¹ The percentage for the breakdown of reasons for discontinuation is calculated over the total number of subjects discontinuing the study.

² The percentage for the breakdown of reasons for discontinuation of study drug is calculated over the total number of subjects discontinuing the study drug.

Protocol Violations/Deviations

The Applicant's Position:

A total of 48% of the subjects (12 of 25) had major protocol deviations during the period covered by the trial report. The most common major protocol deviations were pharmacokinetic sampling performed out of window or missed (three subjects), bone marrow biopsies/aspirates performed out of window or missed (two subjects), and deviations to eligibility criteria (two subjects). All other deviations occurred in only one subject each. No deviations affected a subject's eligibility for the FAS.

The FDA's Assessment:

FDA agrees with the description of protocol violations and disposition above. Additional information was requested regarding two eligibility criteria deviations as described below. Ultimately FDA agrees that eligibility for the FAS was not affected by these protocol deviations.

- Patient (b) (6) was initially diagnosed with INSS stage 1 NB and MYCN non-amplification and did not meet high-risk criteria at the time of diagnosis; a protocol deviation was recorded. However, after diagnosis and before enrollment on Trial 201, the patient demonstrated metastatic recurrence and was started on treatment as per COG study ANBL0532 for high risk neuroblastoma and was refractory to this treatment (considered primary refractory).

{DANYELZA, naxitamab-gqgk}

- Patient (b) (6) was noted to have an eligibility criteria protocol violation. The patient was diagnosed in China originally and not diagnosed according to INRC criteria. According to the Applicant, the patient had Stage 3 disease at the time of diagnosis, and Stage M (secondary refractory disease in bone and bone marrow, having received chemotherapy at the time of diagnosis of metastatic disease) at the time of enrollment in Trial 201.

The reviewer considers that these patients appear to be eligible for the study despite being recorded as eligibility criteria deviations.

Table of Demographic Characteristics

The Applicant's Position:

Baseline demographics are shown in Table 8-8, and baseline disease characteristics are summarized after the table.

Table 8-11 Summary of Baseline Demographics, Trial 201, Cohort 1 FAS

Characteristic	Statistic/Category	Trial 201 Cohort 1 FAS
Subjects	N	22
Age at enrollment (y)	Mean $\pm$ SD	5.6 $\pm$ 1.97
	Median	5.0
	Min, max	3, 10
Sex	Females (%)	9 (40.9%)
	Males (%)	13 (59.1%)
Race	White (%)	10 (45.5%)
	Asian (%)	11 (50.0%)
	Other (%)	1 (4.5%)
Ethnicity	Hispanic or Latino (%)	2 (9.1%)
	Non-Hispanic or Latino (%)	16 (72.7%)
	Not Reported	3 (13.6%)
	Missing	1 (4.5%)
Height (cm)	Mean $\pm$ SD	115.8 $\pm$ 13.84
	Median	112.5
	Min, Max	97, 153
Weight (kg)	Mean $\pm$ SD	20.57 $\pm$ 7.90
	Median	17.6
	Min, Max	11.8, 42.2

Max = maximum; Min = minimum; FAS = full analysis set.

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

{DANYELZA, naxitamab-gqgk}

The subjects in the Cohort 1 FAS population comprised high-risk neuroblastoma subjects with primary refractory disease (14 subjects, 63.6%) or incomplete response to salvage treatment (8 subjects, 36.4%) in bone and/or bone marrow.

In conclusion, the subject population is considered representative for the high-risk neuroblastoma population, thereby providing relevant support to the results of the pivotal Trial 12-230.

The FDA's Assessment:

FDA generally agrees with the description of baseline characteristics above. Patients had disease in the bone (59%), bone marrow (9%) or both (32%). All patients had received prior chemotherapy (100%), 91% had received prior surgery, 36% had received prior radiation, 18% had received prior anti-GD2 therapy and 18% had received a prior autologous stem cell transplant. 86% had Stage 4 disease and 18% had MYCN amplification or gain (59% did not have MYCN gain or amplification and 23% were not reported). Among patients with relapsed disease (n=8), patients had received a median of 2 lines of prior therapy (range 2 to 3).

FDA notes that patients included in the interim efficacy analysis were enrolled at three sites: Memorial Sloan Kettering (n=8), Riley Hospital for Children (n=1) and Hospital Sant Joan de Deu (n=16). See description of post-marketing requirements in Section 13 regarding the need for additional sites for evaluation of safety and efficacy.

FDA requested additional, detailed information regarding prior therapy and the timing of receipt of such therapy received by patients included in the efficacy population in order to better characterize the study population and any potential impact of prior treatment on the assessment of efficacy of naxitamab. The Applicant provided a detailed listing of therapies received, the response to such therapies as available, and the timing with respect to enrollment on Trial 201. FDA's analysis of the study population indicated that three responders in Trial 201 (subject IDs (b) (6)) received chemotherapy within 30 days of enrollment (17, 28, and 28 days, respectively). Refer to the description of a sensitivity analysis with respect to the interval of time between discontinuation of prior treatment to acquisition of the baseline scan in the description of the results of the primary endpoint.

{DANYELZA, naxitamab-gqgk}

Table 8-12: Responding Patients with Baseline Disease Assessments Less than Four Weeks from Prior Systemic Therapy in Trial 201

Subject ID	Disease Status	Last systemic therapy prior to enrollment on Study 12-230	Response to prior therapy, if available	Duration from end of systemic therapy to baseline disease assessment	Response/ Duration of Response to Naxitamab
(b) (6)	Primary refractory	Cyclophosphamide, doxorubicin, vincristine Duration: 5 days, preceded by 3 cycles multiagent chemotherapy	Not provided	3.1 weeks	CR, 20.4 weeks
(b) (6)	Primary refractory	MKSCC protocol 00-065: vincristine, doxorubicin, cyclophosphamide, cisplatin and etoposide Duration: Approximately 4 months	Not provided	2.6 weeks	CR, 24.9 weeks
(b) (6)	Primary refractory	Cyclophosphamide, topotecan, cisplatin, etoposide, doxorubicin and vincristine per ANBL 0532 Duration: Approximately 4 – 5	Not provided	2.9 weeks	CR, 23 weeks

{DANYELZA, naxitamab-gqgk}

Subject ID	Disease Status	Last systemic therapy prior to enrollment on Study 12-230	Response to prior therapy, if available	Duration from end of systemic therapy to baseline disease assessment	Response/ Duration of Response to Naxitamab
		months			
(b) (6)	Primary refractory	Cyclophosphamide, topotecan Duration: 1 week	Not provided	1.9 weeks	PR, 25 weeks
(b) (6)	Incomplete response to salvage treatment	Cyclophosphamide, topotecan Duration: 5 days, preceded by one cycle multiagent chemotherapy	Stable disease	1.7 weeks	CR, 23.9 weeks
Unconfirmed Responses					
(b) (6) (not responder in FDA analysis)	Incomplete response to salvage therapy	Cyclophosphamide, topotecan Duration: 1 month	Not provided	1.6 weeks	
(b) (6) (not responder in FDA analysis)	Primary refractory	Cyclophosphamide, topotecan Duration: 5 days, preceded by 2 months multiagent chemotherapy	Not provided	3 weeks	
(b) (6) (not	Primary	Cisplatin and	Partial	2.4 weeks	

{DANYELZA, naxitamab-gqgk}

Subject ID	Disease Status	Last systemic therapy prior to enrollment on Study 12-230	Response to prior therapy, if available	Duration from end of systemic therapy to baseline disease assessment	Response/ Duration of Response to Naxitamab
responder in FDA analysis)	refractory	etoposide Duration: 5 days, preceded by ~ 4 months multiagent chemotherapy	response		
(b) (6) (not responder in FDA analysis)	Incomplete response to salvage treatment	Vindesine (vinca alkaloid), irinotecan, cyclophosphamide Duration: 4.5 week course	Not provided	2.4 weeks	
(b) (6) (not responder in FDA analysis as not confirmed)	Incomplete response to salvage treatment	Cyclophosphamide, topotecan Duration: ~ 1 moth, preceded by one cycle multiagent chemotherapy	Not provided	2.1 weeks	

Source: Primary review, Response to FDA Information Request

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment compliance

All investigational products were prepared and administered in-clinic. Approximately 97% of

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

{DANYELZA, naxitamab-gqgk}

the actual doses of Naxitamab was equal to the planned dose.

Concomitant medications

Treatment, considered necessary for the subject's wellbeing (including supportive care) and not interfering with the assessment of safety and efficacy of the investigational treatment, was allowed at the discretion of the investigator.

A premedication scheme was recommended to mitigate expected AEs, including pain associated with infusion of naxitamab.

Pretreatment before naxitamab infusions included analgesics for pain (e.g., hydromorphone), corticosteroids, antipyretics (acetaminophen), antihistamines (e.g., diphenhydramine or hydroxyzine), and antiemetics (e.g., ondansetron).

During treatment, the following therapies were not allowed:

- Any additional systemic anticancer therapy
- Any local radiotherapy not predefined at baseline
- Any live vaccines
- Intravenous immunoglobulin
- Any investigational medicinal product not defined in the protocol

No major protocol deviations due to the use of prohibited concomitant medications were reported in the trial.

Rescue Medication

Radiotherapy to primary site

For subjects who were enrolled without having previously received external-beam radiotherapy to the primary site, this standard consolidative therapy for high-risk NB should be performed prior to the screening MIBG/PET scans. In circumstances where the subject was in a critical state with an urgent need of systemic treatment from this trial protocol, the subject could receive the standard consolidation radiotherapy to the primary site, after completion of at least one treatment cycle, preferably between Cycle 1 and Cycle 2. The site for external beam radiotherapy to the primary tumor site was to be predefined and recorded in the CRF at baseline.

Radiotherapy to metastatic sites

{DANYELZA, naxitamab-gqgk}

In circumstances where the subject was in a critical state with an urgent need of systemic treatment, the subject was allowed to receive external-beam radiotherapy for sites with bulky/measurable bony metastasis. The radiation should be given after completion of at least one treatment cycle, preferably between Cycle 1 and Cycle 2. The metastatic lesions for external beam radiotherapy was to be predefined and recorded in the CRF at baseline. It was a requirement that the subject had evaluable disease outside the radiation areas to be eligible for the trial.

No major protocol deviations due to the use of rescue medication were reported.

The FDA's Assessment:

In Trial 201, the protocol recommended treatment for up to 101 weeks; patients who demonstrate a response were to receive naxitamab cycles every 4 weeks until 5 cycles after demonstration of a response, followed by cycles every 8 weeks. Of the 14 responding patients as of the original data cut-off for the application (June 12, 2019), 7 patients had at least five cycles of treatment after the onset of response, 3 patients discontinued before reaching 5 cycles after response due to adverse events or progressive disease, and 4 patients had treatment ongoing. No patients had received 101 weeks of treatment with naxitamab.

FDA performed an evaluation of the receipt of radiotherapy relative to responses observed in the trial. A total of 6 of 22 (27%) patients received radiation while on treatment with naxitamab: 4 patients received radiotherapy to the primary site of disease (e.g., abdominal tumor bed) prior to demonstrating a response to naxitamab (although per the Applicant, the primary site of disease could not represent a target lesion as soft tissue tumors were not permitted to be primary lesions), 1 patient received radiation after achieving an objective response to naxitamab (patient (b) (6), summarized below) and 1 patient did not demonstrate a response to naxitamab.

- (b) (6): Patient initiated naxitamab in (b) (6), demonstrated CR in (b) (6), and received radiation in (b) (6). The Applicant reported that this patient did not demonstrate disease progression prior to receipt of radiation, but received radiation to the primary tumor because the patient had not yet received radiation typically administered as part of multiagent first-line therapy.

Reviewer note: The patient appears to have received radiation to a non-target lesion which would not be expected to impact assessment of response.

{DANYELZA, naxitamab-gqgk}

Overall, the reviewer assesses that given the limitation of radiation to non-target lesions, the receipt of radiation is not expected to have contributed to the objective responses observed in the study.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

The 22 subjects in Cohort 1 included in the FAS were evaluated for the primary and secondary efficacy endpoints.

The efficacy results from the interim analysis are promising and provide supportive evidence obtained in a multicenter setting that naxitamab treatment is effective in subjects with refractory or relapsed neuroblastoma in bone and/or bone marrow.

Overall Response Rate (ORR)

This section was deleted given inconsistency with the FDA analysis due to including unconfirmed responses.

The FDA's Assessment: FDA does not agree with the primary efficacy analyses results. Treatment with naxitamab in combination with GM-CSF lead to an ORR of 45% (95% CI: 24, 68%). FDA considers that patient (b) (6), who received chemotherapy 1.6 weeks after onset of objective response, does not have a confirmed response that reflects the effect of naxitamab monotherapy, and will not be considered a responder. In addition, only confirmed responses are considered. The primary efficacy result is summarized in the following table.

Table 8-13 Summary of Overall Response Rate, Trial 201

Best Overall Response	Primary Efficacy Population (N = 22)
Overall response rate, n (%)	10 (45)
Clopper-Pearson 95% CI	(24, 68)
Complete Response, n (%)	8 (36)
Partial Response, n (%)	2 (9)

Source: FDA reviewer-generated table using data submitted by Applicant for Trial 201 (ADRESP)

{DANYELZA, naxitamab-gqgk}

There were several review issues in FDA's evaluation of the primary endpoint, including the method for determining the overall response by INRC, the method of handling soft tissue disease in the assessment according to the INRC, and the assessment potential confounding of the efficacy results due to a short interval between prior systemic therapy and the baseline scan for Trial 201.

Review Issue: Assessment of Overall Response per INRC

Individual components of the responses used to generate the INRC assessment (measurement of soft tissue lesions, bone marrow evaluations, and MIBG/FDG evaluations) were independently reviewed and the charter for the independent review was included in the BLA. The assessment of overall response per the INRC was made by the Applicant based on the independently reviewed components. During the review, FDA requested detailed listings including information about the inclusion of soft tissue lesions in the overall assessment of response and reviewed the overall response assessments made by the Applicant.

Reviewer assessment: The reviewer considered that the overall response per INRC as determined by the Applicant was acceptable in the context of this trial.

Review Issue: Assessment of Soft Tissue Lesions

The Applicant provided an overview of response assessment in soft tissue lesions. The Applicant stated that exclusion of patients with soft tissue disease at baseline was at the investigator's discretion, although the eligibility criteria excluded patients with soft tissue disease. The Applicant stated that patients with soft tissue disease expected to be scar tissue were permitted to enroll. Baseline soft tissue disease was followed by CT/MRI and evaluated independently, but the external radiology review was not asked to assess whether disease represented active tumor, and MIBG/PET results have not been considered in the assessment of soft tissue according to the review charter.

Reviewer note: The INRC assessment of soft tissue disease incorporates use of MIBG/FDG for assessment of response and in defining target lesions. FDA requested additional information including baseline FDG avidity in soft tissue lesions to assess the

APPEARS THIS WAY ON
ORIGINAL

Local radiotherapy was permitted to soft tissue disease present at baseline during the trial, and as soft-tissue responses were not incorporated into the overall response assessment by INRC since these were not considered target lesions, radiation is not expected to contribute to the responses observed. The development of new soft tissue lesions or progression in existing soft

{DANYELZA, naxitamab-gqgk}

tissue disease was assessed and, if present, would result in an overall assessment of progressive disease as per the revised INRC.

Below is a summary of each patient with soft tissue disease at baseline or during the trial, and an assessment of how this impacted FDA's assessment of overall response.

Patients with Soft Tissue Lesions at Baseline:

- Patient (b) (6): This patient had baseline STL which was irradiated. This patient received radiation to the primary site of disease shortly after initiating treatment with naxitamab. The patient demonstrated a complete response to naxitamab based on response in bone (bone marrow not involved). Soft tissue disease outside the primary site was not reported.
- Patient (b) (6): This patient had baseline STL which was irradiated. This patient received radiation to the primary site of disease shortly after initiating treatment with naxitamab. The patient demonstrated a complete response to naxitamab. Soft tissue disease outside the primary site was not described by the Applicant.
- Patient (b) (6): : This patient had baseline STL which was irradiated. This patient received radiation to the primary site of disease shortly after initiating treatment with naxitamab. The patient demonstrated a partial response to naxitamab. Soft tissue disease outside the primary site was not described by the Applicant.
- Patient (b) (6): : This patient had baseline STL which was irradiated. This patient received radiation to the primary site of disease shortly after initiating treatment with naxitamab. Soft tissue disease outside the primary site was not described by the Applicant. This patient demonstrated an initial complete response in bone marrow and bone, but the responses were not confirmed by a subsequent assessment and therefore was not considered a responder in the FDA analysis.

{DANYELZA, naxitamab-gqgk}

- Patient (b) (6): The subject had a record of STL at baseline which was not irradiated on study and developed a new STL at Week 26, although the baseline soft tissue tumor appears to have resolved by Week 26. The patient had a CR in the bone at Week 6, at which time the baseline STL lesion was not evaluable; however, the CR was not confirmed by a subsequent assessment and the patient had PD at Week 18 (and was thus not considered a confirmed responder). Therefore the new STL at Week 26 did not impact response status or DoR.

Reviewer assessment: If one considers the soft tissue lesion present at baseline to have been active disease, a complete assessment of response per INRC at Week 6 cannot be made; in any case, this patient was considered a non-responder in FDA's analysis due to the lack of confirmed response.

Patient (b) (6): The patient had a baseline STL (62 mm) which was irradiated on study and the same lesion at EOT (22.3 mm) resulting in a soft tissue PR at EOT. The lesion was reported as MIBG-avid at baseline; at 6 weeks it was read as "the soft tissue focus more to the left, less active," and at week 18 "mild focus." Based on independent imaging and pathology review of the bone and bone marrow, the Applicant considered the subject to have had a CR at Weeks 6, 18 and 26 but PD (bone and bone marrow) at EOT. At EOT, the STL was described as "more active," which is in alignment with the overall response of PD at EOT.

Reviewer note: Per INRC, overall response of CR requires a CR in all disease compartments; it appears the patient had only a PR (as of end of treatment) in soft tissue. According to the sponsor, the patient received radiation to the primary site of disease after the onset of radiographic response to naxitamab. The sponsor confirmed that Patient (b) (6) would have a response of PR according to INRC but that the assessment of response did not incorporate assessment of the STL. FDA considers that this patient had a response of PR rather than CR, incorporating the response in the soft tissue lesion.

{DANYELZA, naxitamab-gqgk}

- Patient (b) (6): The subject had a record of a baseline STL which was not irradiated and no anatomic imaging for evaluation of the STL at Week 6. Based on independent imaging and pathology review, the patient had a MR at Week 6 as the overall best response; therefore, the STL does not impact response status or DoR.

Reviewer assessment: A complete assessment of response cannot be made in the absence of soft tissue response. However as the patient did not have a PR or CR in the bone or bone marrow, the STL does not affect FDA's assessment of overall response in this patient, or the ORR in the trial.

Patients with Soft Tissue Lesions at Time Points after Baseline:

- Patient (b) (6) (Cohort 2, not included in efficacy FAS): The patient had no baseline STL, but one lesion at EOT, which was after the data cut-off for the ad-hoc interim analysis. Based on independent imaging and pathology review, the patient had PD as best overall response (week 6), so the STL at EOT do not impact the response status.
- Patient (b) (6): The patient had no baseline STL, but three lesions at EOT. Based on independent imaging and pathology review, the patient had CR at Week 6 and Week 18, so STLs at EOT do not impact the response status. Additionally, because the EOT date was after the data cut-off for the ad-hoc interim analysis, these STLs do not impact the calculated DoR.

Reviewer note: This patient received radiation before onset of response, shortly after initiation of study. Radiation was administered to the primary site of disease.

Reviewer assessment: Based upon the review of the cases summarized above, the clinical reviewer concluded that treatment of STL with radiation is not expected to contribute to the overall responses observed. Ultimately, based on the information provided, it appears the approach of not including soft tissue responses in the INRC assessment for lesions are not assessed as active tumor, is acceptable.

Review Issue: Duration from Prior Therapy to Baseline Disease Assessment

FDA considered whether the short time from completion of systemic therapy until the baseline disease assessment could confound the assessment of response to naxitamab. In practice, the urgency to enroll patients, particularly those with primary refractory disease who may have

{DANYELZA, naxitamab-gqgk}

demonstrated stable disease, minor response or partial response to prior intensive chemotherapy, onto a clinical trial may render a standard washout period from completion of prior therapy (i.e., at least 4 weeks prior to baseline disease assessment) challenging. Since patients with progressive disease were excluded from the trial, patients with relapsed disease were treated first with other therapy (typically chemotherapy or chemotherapy and immunotherapy) prior to enrollment, thus the concern that the effect of prior therapy is not reflected in the baseline disease assessment (and thus that responses observed in the trial cannot wholly be attributed to naxitamab) is greater in this population.

In order to address this review issue, FDA performed a sensitivity analysis excluding patients (non-responders and responders) who had a baseline scan < 2.5 weeks from the time of completion of systemic therapy from the efficacy population. In Trial 201, this criterion applied to 2 responders and 4 non-responders, resulting in 8 responders among 16 patients (ORR 50%, 95% CI: 25.5, 74.5), similar to the ORR observed in the overall efficacy population. Because this sensitivity analysis excluded responding patients with durable complete responses which the review team did not consider reasonably attributable to prior therapy, *FDA decided to only exclude those patients who received systemic therapy up until the time of the baseline scan (i.e., those patients with a time from systemic therapy to baseline scan of zero weeks) from the efficacy population; this did not apply to any patients in Trial 201.*

Subgroup analyses

The Applicant's Position:

Subgroup analyses are summarized in Section 8.1.8. Although these supporting subgroup analyses were not powered to show statistical significance, they consistently demonstrated benefit of naxitamab treatment across relevant subgroups.

The FDA's Assessment: FDA conducted additional subgroup analyses by demographic characteristics, as shown in the following table.

{DANYELZA, naxitamab-gqgk}

Table 8-14 Summary of ORR Subgroup Analyses by Demographic Characteristics, Trial 201

	N	ORR, % (95% CI)
Sex		
Female	13	54 (25, 81)
Male	9	33 (7, 70)
Age		
< 6 years	12	42 (15, 72)
6 – 12 years	10	50 (19, 81)
≥ 12 years	0	-
Race, n (%)		
White	10	70 (35, 93)
Asian	11	27 (6, 61)
Other	1	0 (0, 98)

Source: FDA reviewer-generated table using data submitted by Applicant for Trial 201 (ADRESP)

Table 8-15 presents the exploratory subgroup analysis of the response rate by both prior anti-GD2 antibody exposure and disease status. Although the number of patients in the subgroups in this analysis are extremely small, as with the corresponding subgroup analysis for Study 12-230, results of this analysis appear to show that there is a trend toward a better response rate in patients with no prior anti-GD2 exposure within the subgroup of patients with relapsed disease.

Table 8-15: Overall Response Rate Subgroups by Anti-GD2 Exposure and Baseline Disease Status in Trial 201

	Prior Anti-GD2	No prior anti-GD2
<i>Incomplete response to salvage therapy</i>		
N	4	4
ORR, % (95% CI)	25 (1, 81)	100 (40, 100)
<i>Primary refractory</i>		
N	0	14
ORR, % (95% CI)		57 (29, 82)

Source: FDA reviewer-generated table using data submitted by Applicant for Trial 201 (ADRESP)

Data Quality and IntegrityThe Applicant's Position:

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

{DANYELZA, naxitamab-gqgk}

The results from the performed data quality assurance procedures yielded no reason for concerns.

The FDA's Assessment:

Multiple information requests were required regarding the datasets to support the BLA as a whole, given the use of atypical variables and the datasets missing important flags or variables.

Efficacy Results – Secondary and other relevant endpoints

Duration of response (DoR)

The Applicant's Position:

This section was deleted given discrepancies from FDA's analysis, which included confirmed responders.

The FDA's Assessment: FDA does not agree with the Applicant's analyses. The median DOR in months is 6.24 (95% CI: 4.90, NE). All responders had an DOR of at least 3 months. The proportion of patients with at least 6 months DOR is 30%. The DOR results are shown in **Table 8-16**.

Table 8-16 Summary of Duration of Response, Trial 201

	Responders (N = 10)
Duration of Response	
Median, months (95% CI)	6.24 (4.9, NE)
Range, months	(4.7+, 7.1+)
Percent of responders with DOR ≥ 3 months	100%
Percent of responders with DOR ≥ 6 months	30%

+: censored; NR: Not reached; NE: Not estimable;

Source: FDA reviewer-generated table using data submitted by Applicant for Trial 201 (ADRESP)

Given the high number of patients censored for DoR, FDA requested narratives describing the reason for censoring and any subsequent disease assessments and alternative anticancer

{DANYELZA, naxitamab-gqgk}

therapy. This information is summarized in Table 8-17.

Table 8-17: Summary of Duration of Response Data including Assessments after End of Treatment (Data cut-off 7/23/2020)

Subject ID	Best Overall Response/DoR per Applicant's Analysis	Follow-up Narrative and FDA Reviewer Comments
(b) (6)	Complete Response/ 20.4 weeks	Last evaluation week 28.3 Received alternative anticancer treatment (bivalent vaccine) starting week 30.6
(b) (6)	Complete Response/ 0 weeks	Discontinued week 8.1 due to adverse event <i>Reviewer note: Upon review, this patient did not have a confirmed response of CR, and was therefore considered a non-responder in FDA's efficacy analysis.</i>
(b) (6)	Complete Response/ 24.9 weeks	Progressive disease week 31.1 Received alternative anticancer treatment (bivalent vaccine) starting week 35.6
(b) (6)	Complete Response/ 11.1 weeks	Completed treatment week 25.3 Received alternative anticancer treatment (bivalent vaccine) starting week 30.3
(b) (6)	Partial Response/ 14.7 weeks	Completed treatment week 46.7, last assessment "not evaluable." No clinical assessments in long-term follow-up as of DCO
(b) (6)	Complete Response / 12.1 weeks	Completed treatment week 24.7 with investigator-assessed CR

{DANYELZA, naxitamab-gqgk}

Subject ID	Best Overall Response/DoR per Applicant's Analysis	Follow-up Narrative and FDA Reviewer Comments
		Independent review demonstrated PD at week 18 Received alternative anticancer treatment (bivalent vaccine) starting week 28.6 <i>Reviewer note: Upon review, this patient did not have a confirmed response of CR, and was therefore considered a non-responder in FDA's efficacy analysis.</i>
(b) (6)	Complete Response/ 11.7 weeks	Progressive disease week 24.7 Received alternative anticancer treatment (surgery, chemotherapy, omburtamab, and naxitamab) starting week 27.6 <i>Reviewer note: Upon review, this patient did not have a confirmed response of CR, and was therefore considered a non-responder in FDA's efficacy analysis.</i>
(b) (6)	Complete Response/ 27.1 weeks	Completed treatment week 24.7, progressive disease week 32.7 Received alternative anticancer therapy (radiation, HITS protocol) starting week 29.4
(b) (6)	Complete Response/ 31 weeks	Completed treatment per protocol week 24.7, last independent disease assessment week 36.3 Received alternative anticancer therapy (radiotherapy) trial week 32.3 <i>Site queried regarding RT; patient received RT to rib to 'consolidate refractory site.' At baseline the</i>

{DANYELZA, naxitamab-gqgk}

Subject ID	Best Overall Response/DoR per Applicant's Analysis	Follow-up Narrative and FDA Reviewer Comments
		<i>patient had disease in the bone marrow and pelvis.</i>
(b) (6)	Complete Response/ 21.3 weeks	Disease progression week 26.7 <i>Reviewer note: In a response to an information request, the sponsor noted that the DoR should be censored at week 18 (from initial response at week 6). The DoR should therefore be 12 weeks. In addition, the confirmatory assessment at 18 weeks was a PR (not a CR), so the confirmed response was considered as a PR.</i> Received alternative anticancer therapy (radiotherapy, HITS protocol) starting week 23.4
(b) (6)	Complete Response / 24.9 weeks	Progressive disease week 30 Received alternative anticancer therapy (radiotherapy, HITS protocol) starting week 34.1
(b) (6)	Complete Response/ 18.9 weeks	Completed treatment week 32.7 Adjudicated response demonstrated PD at week 26 <i>Reviewer note: Upon review, this patient was not evaluable at Week 14 on study after demonstrating CR at Week 6. At Week 14, the patient's bone imaging was not available. The subsequent evaluation at Week 26 demonstrated PD. This patient did not have a confirmed response of CR, and was therefore considered a non-responder in FDA's efficacy analysis.</i>

{DANYELZA, naxitamab-gqgk}

Subject ID	Best Overall Response/DoR per Applicant's Analysis	Follow-up Narrative and FDA Reviewer Comments
(b) (6)	Complete Response/ 27.7 weeks	Completed treatment according to protocol week 44.7 Last assessment week 45.3 (CR), no progressive disease as of week 68.3
(b) (6)	Partial Response/ 1.6 weeks	Progressive disease week 4.7 Received HITS protocol week 7.1 to 41.1 <i>Reviewer note: Upon review, this patient received chemotherapy shortly after the first response assessment, and therefore did not have a confirmed response attributable solely to naxitamab. FDA considered this patient a non-responder</i>
(b) (6)	Complete Response/ 23.9 weeks	Completed treatment week 24.7 Last disease assessment (CR) week 29.4. Radiotherapy received week 30.1

Source: FDA primary clinical review, sponsor response to information request

Dose/Dose Response

The Applicant's Position:

All subjects were treated at the same dose level and regimen.

The FDA's Assessment:

FDA has no additional comments.

Durability of Response

The Applicant's Position:

{DANYELZA, naxitamab-gqgk}

This is addressed under the secondary endpoint, Duration of Response, above.

The FDA's Assessment:

FDA has no additional comments. See discussion above.

Persistence of Effect

The Applicant's Position:

This is addressed under the secondary endpoint, Duration of Response, above. No long-term efficacy data with the exception of those presented in the preceding sections are available at the time of this application.

The FDA's Assessment:

FDA agrees that data on persistence of effect following discontinuation of naxitamab is not available beyond the duration of response data described.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Not applicable

The FDA's Assessment:

Patient-reported outcome data was not collected on Trials 12-230 or 201.

{DANYELZA, naxitamab-gqgk}

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA has no further comments.

8.1.5. Retrospective Study 2PR01

The Applicant's Description:

Trial Design

Study 2PR01 is a retrospective, noninterventional, noncomparative, single-center, observational study in patients with high-risk neuroblastoma. The patients were treated in a compassionate-use program for named patients. The study was a medical records review, where data were collected from patient medical records and recorded in eCRFs. The objectives were to evaluate the safety and efficacy of naxitamab + GM-CSF and to get an overview of patient characteristics and distribution in the categories of patients treated with naxitamab. The study included 8 categories of patients with neuroblastoma. Categories 1 and 2 (patients with primary refractory disease in bone and/or bone marrow only and patients with relapsed disease with incomplete response to salvage treatment in bone and bone marrow only, respectively) overlap with the subject population in Trials 12-230 and 201. Category 3 (patients with MRD, defined as patients with CR who were MRD positive by qPCR of bone marrow) provide supportive information on the efficacy evaluation of naxitamab. Patients from the remaining categories provide data for the evaluation of the safety of naxitamab.

Trial Location

One site in Spain, Europe.

Choice of Control Group

Since high-risk neuroblastoma is a rare disease, and due to the retrospective character of the study, there was no control group.

{DANYELZA, naxitamab-gqgk}

Diagnostic Criteria

Not applicable due to the retrospective character study design.

Key Inclusion/Exclusion Criteria

To be included in the study, a patient had to meet the following criteria:

- Have a diagnosis of neuroblastoma as defined by international criteria (i.e., histopathology or bone marrow metastases plus high urine catecholamine levels).
- Have been treated with naxitamab + GM-CSF under compassionate use between 01 June 2017 and 30 November 2018.

Dose Selection

All patients included in the application were treated after the same dosing regimen as in Trials 12-230 and 201: the dose level was 9.0 mg/kg per cycle, administered on Days 1, 3, and 5 of each cycle (3.0 mg/kg per infusion) in the presence of s.c. GM-CSF (Days –4 through 5).

Study Treatments, Treatment Assignment, and Blinding

For patient categories 1, 2 and 3, treatment was in accordance with the trials 12-230 and 201, at the discretion of the investigator.

Dose Modification, Dose Discontinuation

For patient Categories 1, 2, and 3, this was in accordance with the Trials 12-230 and 201, at the discretion of the investigator.

Administrative Structure

This retrospective study was sponsored by Y-mAbs Therapeutics. Y-mAbs used CROs to monitor study data collected from patient records selected under the protocol criteria, to provide EDC and data management services, and to conduct the statistical analysis.

Procedures and Schedule

For patient Categories 1, 2, and 3 procedures and schedule were in accordance with the Trials 12-230 and 201, at the discretion of the investigator.

{DANYELZA, naxitamab-gqgk}

Study Endpoints

Patient Categories 1 and 2, pooled: Overall response rate (ORR), defined as the sum of PR and CR, supported by DoR. Investigator-assessed responses were used for response evaluations.

Patient Category 3: The proportion of patients with MRD at baseline who convert from positive to negative.

Statistical Analysis Plan and Amendments

A standalone SAP was made for the analyses performed to support the BLA. There is only one version of the SAP. The SAP was signed before the statistical analyses of efficacy started. The principal features in the SAP followed the ones in the protocol. The SAP deviated from the protocol in the following feature:

The duration of response was not specified as an efficacy endpoint in the protocol and was added as an exploratory endpoint in this SAP.

The analyses performed followed the SAP.

Efficacy analysis

Patients could enroll more than once to compassionate-use treatment and could have different disease profiles at different enrollments. However, in the patient Categories 1 and 2, there were 6 unique patients, and in patient Category 3, there were 13 unique patients (i.e., all only enrolled once).

The full analysis set (FAS) comprised the pooled Categories 1 and 2 encompassing 6 enrollments (6 unique patients). In addition, for Category 3, efficacy data on MRD was evaluated as supportive evidence for the effect of naxitamab. The Category 3 FAS comprised 13 enrollments (13 unique patients).

Safety analysis

Safety analyses are defined and presented in Section 8.2.

PK analysis

Not applicable.

{DANYELZA, naxitamab-gqgk}

Protocol Amendments

The study protocol was amended once during the study. None of the implemented changes impacted the integrity of the trial or the interpretation of the results. This amendment added the section on monitoring and quality assurance.

The FDA's Assessment:

As previously stated, FDA does not consider this retrospective study to provide substantive information to support the safety and effectiveness of naxitamab in this application. FDA considers that the retrospective nature of the study may lead to incomplete data collection that renders interpretation of the results of the study difficult. Further, the efficacy results were determined by investigator assessment rather than independent central review, which FDA generally recommends for assessment of ORR in single arm trials to minimize the potential for bias.

8.1.6. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

Data entry for this retrospective observational study was done in accordance with the protocol, the principles of the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines for data entry and monitoring, and with the laws and regulations in Spain.

The FDA's Assessment:

FDA has no additional comments.

Financial Disclosure

The Applicant's Position:

Refer to Section 19.2.

The FDA's Assessment:

There were no relevant financial disclosures for this study.

{DANYELZA, naxitamab-gqgk}

Patient Disposition

Six patients in Categories 1 and 2, pooled (overlap the subject population in Trials 12-230 and 201) and 13 patients in Category 3 were included in the efficacy evaluation since they provide supportive information on the efficacy of naxitamab. Four of the six patients in Categories 1 and 2 discontinued due to progressive disease and four of the 13 patients in Category 3 discontinued because their treatment was completed.

Protocol Violations/Deviations

The Applicant's Position:

Protocol deviations are not relevant for this retrospective study.

The FDA's Assessment:

FDA has no additional comments.

Table of Demographic Characteristics

The Applicant's Position:

In the retrospective Study 2PR01, there were 6 patients in the categories overlapping the populations in Trial 12-230 and Trial 201 (Categories 1 and 2). In these groups, the ages ranged from 4 to 16 years, with a mean (SD) age of 8.8 (4.5) years. Body weight ranged from 20 to 57 kg, with a mean (SD) body weight of 30.6 (14.1) kg. Four patients were female, and two were male. Five patients were White and one was Chinese. This population had an older mean age, but similar age range as in Study 12-230.

There were 13 patients in Category 3. The ages ranged from 2 to 6 years, with a mean age (SD) of 3.4 (1.2) years. Body weight ranged from 11 to 21 kg, with a mean (SD) body weight of 16.2 (3.4) kg. Three patients were female, and 10 were male. Three patients were White and nine were Chinese.

Categories 1 and 2 had two patients with primary refractory disease status of baseline and four patients with incomplete response to salvage therapy.

The FDA's Assessment:

FDA did not perform dedicated analyses for this study. As previously stated, FDA does not consider this retrospective study to provide substantive information to support the

{DANYELZA, naxitamab-gqgk}

safety and effectiveness of naxitamab in this application. FDA considers that the nature of the study may lead to incomplete data collection that renders interpretation of the results of the study difficult.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment compliance

Not evaluated.

Concomitant medications

Not evaluated.

Rescue medication

Not evaluated.

The FDA's Assessment:

FDA has no additional comments.

Efficacy Results

The Applicant's Position:

The efficacy results from retrospective Study 2PR01 using investigator-based assessments support the use of naxitamab as an efficacious treatment of patients with primary refractory disease or incomplete response to salvage treatment in bone and/or bone marrow.

Categories 1 and 2

Treatment with naxitamab in combination with GM-CSF in patients with primary refractory disease or incomplete response to salvage treatment in bone and/or bone marrow only, led to an objective response of 66.7% (4 of 6 patients) (95% CI: 22.3%, 95.7%), see Table 8-18. Two enrollments had complete response, two had partial response, and two had progressive

{DANYELZA, naxitamab-gqgk}

disease. The median duration of response was not estimable due to ongoing responses in 2 of 4 patients (95% CI: 7.9, not estimable).

Category 3

Of the 13 enrollments in Category 3, seven (53.8%, [95% CI: 25.1%, 80.8%]) patients experienced a conversion from MRD positive to MRD negative, Table 8-19.

Table 8-18 Summary of Efficacy Analysis for 2PR01, Pooled Categories 1 and 2, Full Analysis Set

Categories 1, 2 (pooled): 1° refractory disease/incomplete response to salvage treatment in bone and/or BM only		
Patient Enrollments	N	6
Evaluable patients with response data	N (%)	6 (100)
Objective response rate (CR+PR)	N (%)	4 (66.7)
	95% CI	22.3, 95.7
Complete response	N (%)	2 (33.3)
Partial response	N (%)	2 (33.3)
Stable disease	N (%)	0
Progressive disease	N (%)	2 (33.3)
Duration of response (weeks) - Kaplan-Meier estimates	N (%)	4 (66.7)
	Median	NE
	95% CI	7.9, NE

BM = bone marrow; CI = confidence interval; CR = complete response; NE = not estimable; PR = partial response; SD = standard deviation.

Table 8-19 Summary of Efficacy Analysis for 2PR01, Category 3, Full Analysis Set

Category 3: MRD, positive by qPCR of BM		
Patient Enrollments	N	13
Proportion converting from MRD+ to MRD-	N (%)	7 (53.8)
	95% CI	25.1, 80.8

BM = bone marrow; CI = confidence interval; MRD+ = positive for minimal residual disease; MRD- = negative for minimal residual disease; qPCR = quantitative real-time polymerase chain reaction.

Subgroup analyses

The Applicant's Position:

No subgroup analyses were performed.

Data Quality and Integrity

{DANYELZA, naxitamab-gqgk}

The Applicant's Position:

The results from the performed data quality assurance procedures yielded no reason for concerns.

The FDA's Assessment:

FDA did not perform dedicated analyses for this study. As previously stated, FDA does not consider this retrospective study to provide substantive information to support the safety and effectiveness of naxitamab in this application. FDA considers that the nature of the study may lead to incomplete data collection that renders interpretation of the results of the study difficult. Specific issues include the lack of efficacy data for all patients and the lack of independently reviewed efficacy data. Blinded, independent, central review is the standard for assessment of ORR and DOR in single arm trials used to support marketing applications.

Dose/Dose Response

The Applicant's Position:

All subjects were treated at the same dose level and regimen.

The FDA's Assessment:

FDA has no additional comments.

Durability of Response

The Applicant's Position:

This is addressed above.

The FDA's Assessment:

FDA did not confirm analyses of efficacy or safety for this study.

Persistence of Effect

The Applicant's Position:

This is addressed above. No long-term efficacy data with the exception of those presented in

the preceding sections are available at the time of this application.

The FDA's Assessment:

FDA did not confirm analyses of efficacy or safety for this study.

8.1.7. Integrated Review of Effectiveness

The FDA's Assessment:

The clinical and statistical review teams conclude that taken together, the data from Study 12-230 and Study 201 provide substantial evidence of the effectiveness of naxitamab, in combination with GM-CSF, in pediatric and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a response of stable disease or better to prior therapy.

Data to Support Contribution of Effect of GM-CSF

The Applicant, at FDA's request, provided rationale to support the contribution of effect of sargramostim (GM-CSF) to the proposed regimen. GM-CSF is currently approved for multiple indications with a recommended dose of 250 mcg/m²/day administered intravenously or subcutaneously; the dose for the indication "BMT [bone marrow transplantation] failure or engraftment delay," suggests a third course of 500 mcg/m²/day can be used for 14 days in the event neutrophil recovery has not occurred with two courses of 250 mcg/m²/day for 14 days. The Applicant cites literature supporting the role of GM-CSF in combination with immune therapy to enhance cell-mediated cytotoxicity, as well as the approval of dinutuximab in combination with IL-2 and GM-CSF in patients with neuroblastoma.

The Applicant provided results from MSK which tested mu3F8 and GM-CSF in different combinations in vitro, demonstrating that mu3F8 mediated granulocyte antibody-dependent cellular cytotoxicity (ADCC) in a dose-dependent manner with maximal lysis at 10 µg/mL and half-maximal lysis at 0.1 µg/mL. (Kushner and Cheung, 1989) Adding GM-CSF translated to a tenfold or greater reduction in the concentration of mu3F8 required for mediating granulocyte ADCC. Table 8-18, which includes data from the referenced publication, was provided by the Applicant in support of the contribution of effect of GM-CSF.

{DANYELZA, naxitamab-gqgk}

Table 8-20: GM-CSF Enhancement of mu3F8–Mediated Granulocyte ADCC

Cell Lines	Mu3F8 (10 µg/mL)		Mu3F8 (1.0 µg/mL)	
	With GM-CSF ^a	Without GM-CSF	With GM-CSF ^a	Without GM-CSF
Neuroblastoma				
NMB-7	4.0	2.9	2.9	1.5
IMR-6	3.1	1.9	2.7	1.2
LAN-1	3.1	1.7	2.6	1.1
LAN-5	1.7	0.7	1.1	0.3
Melanoma				
SK Mel-1	1.9	1.0	1.5	0.7
HT-144	0.9	0.5	0.4	0.2
M-14	0.4	0.2	0.2	0.1

Source: Kushner and Cheung, Blood, 1989

Note: Results are expressed as lytic units/10⁶, and data are the means of three to six experiments. ADCC = antibody-dependent cellular cytotoxicity; GM-CSF = granulocyte-macrophage colony-stimulating factor; mu3F8 = murine 3F8. The GM-CSF concentration was 2 ng/mL.

8.1.8. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:

This Section was deleted given revisions to the efficacy analysis and population described above after discussion with the Applicant.

The FDA's Assessment:

As described in earlier sections, FDA does not agree with the primary efficacy analyses for both Trial 12-230 and Trial 201. In Trial 12-230, the ORR is 34% (95% CI: 20, 51%). In Trial 201, the ORR is 45% (95% CI: 24, 68%).

{DANYELZA, naxitamab-gqgk}

Secondary and Other Endpoints

The Applicant's Position:

This Section was deleted given revisions to the efficacy analysis and population described above after discussion with the Applicant.

The FDA's Assessment:

FDA does not agree with Applicant's description of the results for DOR. The median DOR was not reached for Trial 12-230, and 23% of responders had at least 6 months of ongoing response. In Trial 201, the median was 6.2 months (95% CI: 4.9, NE), and 30% of responders had at least 6 months of ongoing response.

Subpopulations

The Applicant's Position:

Because Trial 12-230 is the only trial included in the BLA with sufficient number of enrollments to explore the effect of naxitamab in subgroups, most subpopulations were only analyzed for the PAS population of Trial 12-230. However, response by disease status (primary refractory or incomplete response to salvage therapy) and response in bone or bone marrow were also analyzed for the FAS of Trial 201. Subgroups that were only investigated in Trial 12-230 were by age, baseline body weight, ADA status, and prior therapy with anti-GD2 therapy.

Response in subgroups by disease compartment and disease status

This Section was deleted given revisions to the efficacy analysis and population described above after discussion with the Applicant.

The FDA's Assessment:

In both Trials 12-230 and 12-201, the subgroup previously treated with GD2 had lower ORR compared with the subgroup without prior GD2. FDA conducted exploratory subgroup analyses of the response rate by both prior anti-GD2 antibody exposure and disease status (incomplete response to salvage therapy vs. primary refractory disease) for both studies (see Table 8-8 and Table 8-15). Although the small sample sizes and exploratory nature of the analyses require cautious, results of these analyses appears to

{DANYELZA, naxitamab-gqgk}

show a trend toward a better response rate in patients with no prior anti-GD2 exposure, part within the subgroup of patients with relapsed disease.

Additional Efficacy Considerations

The FDA's Assessment:

See FDA Assessment in Integrated Assessment of Effectiveness below.

8.1.9. Integrated Assessment of Effectiveness

The Applicant's Position:

Table 8-13 summarizes the key efficacy results from the three trials supporting the use of naxitamab for the treatment of high-risk refractory or relapsed neuroblastoma in bone and/or bone marrow in combination with GM-CSF. In the pivotal Trial 12-230, treatment with naxitamab at greater than or equal to 3.0 mg/kg/d (9.0 mg/kg per cycle) led to a durable, statistically significant ($p=0.0011$) and clinically meaningful ORR of 42.2% in the PAS population, as evaluated by the independent reviewers. The CR rate in the PAS was 31.1%. For enrollments in Trial 12-230 with bone marrow disease at baseline, the CR rate was 80.0% (95% CI: 56.3%, 94.3%).

The robustness of these results is supported by the consistent benefit of naxitamab treatment on ORR in Trial 201, in Study 2PR01, and across subgroups by baseline disease status (primary refractory disease vs. incomplete response to salvage treatment), disease compartment (presence of bone disease vs. bone marrow disease), age, body weight, prior GD2 therapy, and ADA status. Although the supporting analyses by trial and subgroups were not powered to show statistical significance, it is noted that the majority of analyses met the prespecified limit of 20% for the lower bound of the 95% CI.

Overall, the enrollment demographics and baseline disease characteristics for Trials 12-230 and 201 and retrospective Study 2PR01 (Categories 1 and 2) were similar. The trial populations analyzed for efficacy were considered to be sufficiently similar to allow comparison of the efficacy results across the trials. In addition, these demographics are sufficiently representative of the anticipated patient population that will receive the commercial product in the United States.

The subjects included in the primary efficacy analyses received naxitamab in combination with GM-CSF at the planned commercial dose level of 3.0 mg/kg per infusion (9.0 mg/kg per cycle) following the planned commercial regimen of three infusions per cycle on Days 1, 3, and 5 as

{DANYELZA, naxitamab-gqgk}

part of a 4- to 8-week cycle. This dose regimen has been shown in these trials to be effective for the treatment of neuroblastoma in the target patient population.

Taken together, the efficacy data presented in the BLA demonstrate the clinical benefit of naxitamab for the treatment of high-risk refractory or relapsed neuroblastoma in bone and/or bone marrow in combination with granulocyte-monocyte colony stimulating factor (GM-CSF). Treatment with naxitamab can address the significant unmet medical need, providing effective therapy to a patient population currently lacking adequate treatment options.

The FDA's Assessment:

(Note: Table 13 referenced above in the Applicant's position has been removed)

The clinical and statistical review teams concluded that the Applicant has provided substantial evidence of the effectiveness of naxitamab, in combination with GM-CSF, in pediatric and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease, to prior therapy.

This application is supported by evidence of a substantial, clinically meaningful and ORR and durability of responses in this population, which has no approved therapies, in two single-arm trials. In Trial 201 (n=22), the confirmed ORR in patients with metastatic, relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who demonstrated a response of stable disease, partial response, or minor response to prior therapy per blinded, independent review was 45% (95% CI: 24%, 68%), with 30% of the 10 responders having observed duration of response (DOR) of at least 6 months. The primary efficacy analysis in Trial 201 included 4 patients with prior anti-GD2 treatment; one (25%) of these patients demonstrated a response. In Trial 12-230 (n=38), the confirmed ORR per blinded, independent review according to the revised INRC was 34% (95% CI: 20%, 51%), with 23% of the 13 responders having an observed DOR of 6 months. The primary efficacy analysis in Trial 12-230 included 22 patients with prior anti-GD2 treatment; 4 (18%) of these patients demonstrated a response (95% CI 5%, 40%). Given the limited number of patients with prior anti-GD2 exposure, the exploratory analyses of ORR in this subpopulation should be interpreted with caution; however, the results suggest that naxitamab has clinical activity in patients who received prior anti-GD2 antibody therapy.

FDA considers ORR of a sufficient magnitude with a meaningful duration of response as an intermediate endpoint likely to predict clinical benefit in this rare population of patients with relapsed or refractory neuroblastoma in bone or bone marrow who have demonstrated a partial response, minor response or stable disease to prior therapy. Importantly, although the product was studied and is indicated in patients with neuroblastoma in the bone and bone

{DANYELZA, naxitamab-gqgk}

marrow, assessment of responses was performed according to the revised INRC, which incorporates assessment of progression of soft tissue disease and the appearance of any new soft tissue lesions.

It should be noted that patients in both trials were permitted to receive radiation in certain circumstances, as detailed in sections 8.1.2 and 8.1.3, although assessment of response excluded sites that received radiation. Patients who received radiation to the only site of evaluable disease, which occurred only in some patients in Trial 12-230, were excluded from the efficacy analysis. Additionally, patients with a best response of progressive disease to prior therapy (i.e., standard therapy for high-risk neuroblastoma, for those patients with primary refractory disease or salvage therapy at relapse) were excluded from Trial 201 and from the efficacy analysis population in Trial 12-230. Therefore, the indication the review team proposes for approval also excludes these patients.

During the review, the review team considered the impact of a short “wash-out” period between prior systemic therapy and the timing of baseline disease assessments for both studies. FDA considered whether the short time from completion of systemic therapy until the baseline disease assessment could confound the assessment of response to naxitamab. In practice, the urgency to enroll patients, particularly those with primary refractory disease who may have demonstrated stable disease, minor response or partial response to prior intensive chemotherapy, onto a clinical trial may render a standard washout period from prior therapy (i.e., at least 4 weeks prior to baseline disease assessment) challenging and potentially unethical. Since patients with progressive disease were excluded from the trial, patients with relapsed disease were treated first with other therapy (typically chemotherapy or chemotherapy and immunotherapy) prior to enrollment, thus the concern that the effect of prior therapy is not reflected in the baseline disease assessment (and thus that responses observed in the trial cannot wholly be attributed to naxitamab) is greater in this population. FDA performed a sensitivity analysis removing patients with a short interval (< 2.5 weeks) between completion of systemic therapy and baseline disease assessment, which resulted in similar ORRs in comparison to those noted above in both trials, and also resulted in the exclusion of patients with durable complete responses that the review team did not consider reasonably attributable to prior therapy. FDA’s approach was therefore to exclude patients with no washout period between systemic therapy and baseline disease assessments, which applied to one patient in Trial 12-230 as described in the review.

The difference in ORR between Trials 12-230 and 201 may be explained by a higher proportion of patients with relapsed disease, and a higher proportion of patients with prior anti-GD2 therapy, compared to Trial 201; exploratory subgroup analyses in both trials indicated a lower ORR in patients with refractory disease and in patients with prior anti-GD2 therapy. Though the

{DANYELZA, naxitamab-gqgk}

efficacy population across the two studies is relatively small, the review team considers that, based on sustained responses in heavily pre-treated patients with a high unmet medical need, the application warrants accelerated approval.

Information on duration of response is limited by several factors. Neither trial systematically captured imaging assessments after discontinuation of study treatment due to reasons other than disease progression. In addition, some patients who demonstrated a complete response were subsequently treated with additional anticancer therapy to consolidate these responses, which is not an uncommon practice in this disease area given the poor prognosis of subsequent relapses. Duration of response was therefore censored prior to demonstration of disease progression in many patients, and the duration of response in the absence of subsequent therapy is unknown.

Due to small sample sizes and limited follow-up for some patients, there is uncertainty regarding the magnitude and durability of the treatment effect of naxitamab. The review team therefore recommends a postmarketing requirement to verify and confirm the clinical benefit of naxitamab in the indicated patient population by accumulating additional ORR and DOR data across a sufficient number of clinical sites in ongoing Study 201. Postmarketing requirements are described in Section 13.

8.2. Review of Safety

The Applicant's Position:

This safety evaluation is based on data from 273 unique subjects spanning 298 enrollments in four clinical trials and a retrospective study with data collected from subjects treated in a compassionate-use program. Of the 273 unique subjects, 256 subjects were diagnosed with neuroblastoma and 17 subjects were diagnosed with other GD-2-positive malignancies.

- Trial 12-230 (naxitamab + GM-CSF) includes safety data from 117 subjects, spanning 131 enrollments.
- Trial 201 (naxitamab + GM-CSF) includes safety data from 25 subjects.
- Trial 11-009 (naxitamab) includes safety data from 67 subjects (8 of them with other GD2-positive malignancies).
- Trial 12-116 (naxitamab + interleukin) includes safety data from 12 subjects (9 of them with other GD2-positive malignancies).
- Retrospective Study 2PR01 (naxitamab + GM-CSF) includes safety data from 52 patients, spanning 63 enrollments.

{DANYELZA, naxitamab-gqgk}

All clinical trials are single-arm with no comparator, because of the rarity of the disease and the high-risk population involved.

The main focus is on safety data for subjects with neuroblastoma exposed to naxitamab in combination with GM-CSF from Trial 12-230 followed by Trial 201 and 2PR01, then further supplemented by pooled safety data from Trial 12-230 and Trial 11-009 .

Data from these trials allow for an informed assessment of the safety profile of naxitamab in combination with GM-CSF and an evaluation of the overall benefit-risk in subjects with high-risk refractory or relapsed neuroblastoma in bone and/or bone marrow. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

The FDA's Assessment:

FDA considered the analysis of safety to be supported primarily by patients in Trial 12-230 who received the recommended phase 2 dose of naxitamab (n=72) and Trial 201 (n=25). Analyses were also performed for the overall population of patients in Trial 12-230 (n=117) who received any dose of naxitamab, given that some rare infusion-related adverse reactions such as anaphylaxis may not be dose-dependent. Safety data from studies 11-009, 12-116 and 2PR01 was considered supportive and were not included in the primary safety population for FDA's review of the BLA.

8.2.1. Safety Review Approach

The Applicant's Position:

This application is based on a comprehensive analysis of safety data relevant to the use of naxitamab in combination with GM-CSF for the treatment of high-risk refractory or relapsed neuroblastoma in bone and/or bone marrow.

Monoclonal antibody cancer therapies in general have a number of recognized immune-related adverse effects, such as hives, itching, skin rashes, flu-like symptoms, chills, fever, nausea, vomiting, hypotension, bronchospasm, anaphylaxis, and edema, including angioedema. In addition, therapies with anti-GD2 mAbs (e.g., the two marketed anti-GD2 mAbs, Unituxin and Qarziba [dinutuximab beta]), are known to cause pain, hypertension, peripheral neuropathies, accommodation disorder, and mydriasis.

As expected with this class of drugs, clinical experience confirmed that the expected toxicities seen with other anti-GD2 mAbs are also the most frequently observed with naxitamab in combination with GM-CSF.

{DANYELZA, naxitamab-gqgk}

The FDA's Assessment:

FDA's approach to the safety review included evaluation of original datasets including adverse events, vital signs and concomitant medications in addition to safety narratives. See Section 8.2 above regarding the safety population for FDA analyses.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The safety population included all subjects who received naxitamab treatment.

Naxitamab was used in combination with GM-CSF in Trial 12-230, Trial 201, and in 2PR01 patients, as monotherapy in Trial 11-009, and in combination with IL-2 in Trial 12-116.

Safety data comprised 133 subjects with neuroblastoma who received the recommended naxitamab dose level (3 mg/kg/day for a total dose of 9 mg/kg per cycle) in combination with GM-CSF: 72 subjects in Trial 12-230, 25 subjects in Trial 201, and 36 patients in 2PR01.

Exposure to naxitamab was considered appropriate to allow for an adequate assessment of safety in subjects who were representative of the intended target population.

Extent of exposure

Trial 12-230

Trial 12-230 provides the largest source of data for naxitamab exposure. There were 131 enrollments for 117 subjects and all exposed to naxitamab. The mean (SD) number of naxitamab cycles was 4.8 (3.07), ranging from 1 to 15 cycles. For PAS, the mean (SD) number of cycles was 5.6 (2.73), ranging from 1 to 13 cycles.

Trial 201

In Trial 201, 25 subjects were exposed to naxitamab. The mean (SD) number of treatment cycles was 4.6 (2.46), ranging from 1 to 8 cycles.

Trial 11-009

In Trial 11-009, 67 subjects were exposed to naxitamab at doses ranging from 0.06 to

{DANYELZA, naxitamab-gqgk}

3.0 mg/kg/day. The mean (SD) number of treatment cycles was 5.0 (4.33), ranging from 2 to 7 cycles. There were 12 subjects in the 2.6- to 3.0-mg/kg dose group, with a mean (SD) number of treatment cycles of 2.8 (2.18), ranging from 1 to 8 cycles. Of these, 5 subjects were in the 3.0-mg/kg/day dose level.

Trial 12-116

In Trial 12-116, 12 subjects were exposed to naxitamab at doses ranging from 0.3 to 1.2 mg/kg/d. Mean (SD) number of treatment cycles were 2.0 (1.21), ranging from 1 to 4 cycles.

2PR01

In 2PR01, overall, 63 enrollments (52 patients) were exposed to naxitamab, with a mean (SD) number of treatment cycles of 3.7 (2.62), ranging from 1 to 11 cycles. Of these 63 enrollments, 36 enrollments received naxitamab (9.0 mg/kg per cycle) in combination with GM-CSF as per the Protocol 201/12-230 dose regimen.

The FDA's Assessment:

FDA generally agrees with the description of exposure for Trials 12-230 and 201 above, and did not confirm exposure for the subsequently listed supportive trials.

Notably, Trial 12-230 allowed multiple enrollments and the exposure data above reflects data per enrollment. The median number of cycles initiated per enrollment in Trial 12-230 was 4.0 (range 1 – 15, as described above). When considering unique patients enrolled in Trial 12-230 (some of whom were enrolled multiple times), 46% of patients received 5 – 10 cycles, and 17% received 11 or more cycles.

The median number of cycles initiated in Trial 201, which is an ongoing study, was 4 (range 1 – 8). Fifty-two percent of patients received < 5 cycles and 48% received 5 – 8 cycles as of the data cutoff. In Study 201, among 25 patients who received DANYELZA in combination with GM-CSF, 12% were exposed for 6 months or longer and none were exposed for greater than one year.

The reviewer notes that the proposed product label suggests administration of treatment cycles every 4 weeks until CR or PR, then 5 additional cycles. Subsequent optional cycles would be administered every 8 weeks (b) (4). Therefore, a patient receiving naxitamab would be expected to receive > 5 cycles of naxitamab, provided they did not discontinue due to progressive disease or adverse event prematurely. Approximately half of the

{DANYELZA, naxitamab-gqgk}

patients in Trial 201 did not receive the minimum number of cycles proposed in the product label. Data from Trial 12-230 does provide additional data from patients with longer exposures.

Relevant characteristics of the safety population

The Applicant's Position:

The clinical development program has evaluated naxitamab in patients ranging from 1 year of age to 34 years of age, with the vast majority of subjects being pediatric patients 12 years of age or younger. Trial subjects were of diverse ethnic backgrounds and represent a range of baseline disease states, with a majority having refractory or relapsed neuroblastoma in bone and/or bone marrow, thereby providing reassurance regarding the interpretation and the validity of the safety conclusions. Overall, the demographics and baseline disease characteristics of subjects treated in the clinical program reflect the intended target population.

A summary of demographics for the safety population in Trials 12-230, 201, and 2PR01 are shown in Table 8-21.

{DANYELZA, naxitamab-gqgk}

Table 8-21 Demographics and Baseline Characteristics – Trials 12-230, 201, and 2PR01 (SAF)

Characteristic	Statistic/Category	Trial 12-230 (N=131) [n(%)]	Trial 201 (N=25) [n(%)]	2PR01 (N=63) [n(%)]
Age at enrollment (y)	n	131	25	63
	Mean $\pm$ SD	7.0 $\pm$ 4.49	5.4 $\pm$ 2.1	6.6 $\pm$ 5.80
	Median	6.0	5.0	5.0
	Min, max	2, 31	1, 10	1, 31
Sex	Females (%)	51 (38.9%)	9 (36.0)	29 (46.0)
	Males (%)	80 (61.1%)	16 (64.0)	34 (54.0)
Race	White (%)	106 (80.9%)	12 (48.0)	44 (69.8)
	Black or African American (%)	7 (5.3%)	-	-
	Asian (%)	8 (6.1%)	12 (48.0)	17 (27.0%) ^{a)}
	American Indian or Alaska Native (%)	2 (1.5%)	-	-
	Other (%)	2 (1.5%)	1 (4.0)	2 (3.2)
	Not reported (%)	6 (4.6%)	-	-
Ethnicity	Hispanic or Latino (%)	5 (3.8%)	2 (8.0)	17 (27.0)
	Non-Hispanic or Latino (%)	122 (93.1%)	19 (76.0)	44 (69.8)
	Not reported	2 (1.5%)	3 (12.0)	2 (3.2)
	Unknown (%)	2 (1.5%)	1 (4.0)	-
Height (cm)	n	117	25	55
	Mean $\pm$ SD	117 $\pm$ 19.01	114 $\pm$ 14.61	116.5 $\pm$ 22.8
	Median	115	112.0	112.0
	Min, Max	85, 172	83, 153	85, 184
Weight (kg)	n	124	25	55
	Mean $\pm$ SD	23.0 $\pm$ 11.70	20.38 $\pm$ 7.69	23.2 $\pm$ 14.08
	Median	19.9	17.6	18.2
	Min, Max	11, 87	12, 42	11, 79

a) 1.6% Asian and 25.4% Chinese.

Baseline disease characteristics

Of the 273 unique subjects in the safety population, 256 subjects were diagnosed with neuroblastoma and 17 subjects were diagnosed with other GD2-positive malignancies (8 in Trial 11-009, 9 in Trial 12-116).

{DANYELZA, naxitamab-gqgk}

The majority of subjects treated in the clinical development program were diagnosed with high-risk refractory or relapsed neuroblastoma in bone and/or bone marrow.

In the pivotal Trial 12-230, 31.3% of the subjects were diagnosed with an incomplete response to salvage therapy prior to enrollment, and 18.3% had primary refractory disease. The remaining subjects in the pivotal Trial 12-230 did not have evaluable disease and received naxitamab as consolidation therapy and were as such not part of the efficacy population but contribute to the safety population. The Trial 201 population includes 64% subjects with primary refractory disease and 36% with an incomplete response to salvage therapy at enrollment. Study 2PR01 included 8 categories of patients with neuroblastoma. Categories 1 and 2 (6 patients) comprised patients with primary refractory disease in bone and/or bone marrow or relapsed disease with incomplete response to salvage treatment in bone and bone marrow.

The FDA's Assessment:

The following tables with demographic information based on unique patients, not enrollments, for Trial 12-230 was requested by FDA and provided by the Applicant. Data was confirmed by FDA. Per FDA's review there was one patient in Trial 201 with race reported as Black or African American, compared to none in the table below; there were no patients with race reported as other.

Table 8-22: Demographics and Baseline Characteristics – Trials 12-230, 201, and 2PR01 (Unique Subjects in SAF) (Applicant's Analysis)

Characteristic	Statistic	Trial 12-230 All Subjects (N=117) [n(%)]	Trial 201 All Subjects (N=25) [n(%)]	2PR01 All Patients (N=52) [n(%)]
Age (years)	n	117	25	52
	Mean	6.8	5.4	6.1
	SD	4.45	2.1	5.03
	Median	6.0	5.0	5.0
	Q1,Q3	4.0,9.0	-	3, 6.5
	Min,Max	2 , 31	1 , 10	1 , 31
	Female	46 (80.7)	9 (36.0)	22 (42.3)

{DANYELZA, naxitamab-gqgk}

Characteristic	Statistic	Trial 12-230 All Subjects (N=117) [n(%)]	Trial 201 All Subjects (N=25) [n(%)]	2PR01 All Patients (N=52) [n(%)]
Sex	Male	71 (124.6)	16 (64.0)	30 (57.7)
Race	White	93 (163.2)	12 (48.0)	36 (69.2)
	Black or African American	7 (12.3)		-
	Asian	7 (12.3)	12 (48.0)	14 (26.9) ^a
	Hawaiian or other Pacific Islander	0		-
	American Indian or Alaska Native	2 (3.5)	-	-
	Other	2 (3.5)	1 (4.0)	2 (3.8)
	Not Reported	6 (10.5)	-	-
Ethnicity	Hispanic or Latino	4 (7.0)	2 (8.0)	13 (25.0)
	Non Hispanic or Latino	109 (191.2)	19 (76.0)	37 (71.2)
	Not Reported	2 (3.5)	3 (12.0)	2 (3.8)
	Unknown	2 (3.5)	1 (4.0)	-
Height (cm)	n	104	25	46
	Mean	116.68	114.2	115
	SD	19.605	14.605	22.14
	Median	114.45	112	111
	Q1,Q3	102,129.50	-	101, 124
	Min,Max	85.1,171.8	83.0,153.0	85,184
Body Weight (kg)	n	110	25	46
	Mean	22.8	20.38	22.2
	SD	12.073	7.685	13.34
	Median	19.15	17.6	18.0
	Q1,Q3	15.6,25.3	-	15.8, 21.4
	Min,Max	10.7,87.0	11.6,42.2	11,79

Note: Patient counts in the column headers denote the number of unique subjects. Age is age at first enrollment. Enrollment cut-off date for subject population is 15Jan2018. Data cut-off is 15May2018 for efficacy and 17Dec2018 for safety. · 1.9% Asian and 25.0% Chinese.

{DANYELZA, naxitamab-gqgk}

Table 8-23: Summary of Demographics and Baseline Characteristics, Trial 12-230, Patients who Received 3 mg/kg (Applicant's Analysis)

	Statistic	Overall (N=72) [n(%)]
Age (years)	n	72
	Mean	6.5
	SD	4.39
	Median	5.0
	Q1,Q3	3.5,9.0
	Min,Max	2 , 24
Sex	Female	27 (37.5)
	Male	45 (62.5)
Race	White	55 (76.4)
	Black or African American	3 (4.2)
	Asian	5 (6.9)
	Hawaiian or other Pacific Islander	0
	American Indian or Alaska Native	2 (2.8)
	Other	2 (2.8)
	Not Reported	5 (6.9)
Ethnicity	Hispanic or Latino	4 (5.6)
	Non Hispanic or Latino	65 (90.3)
	Not Reported	1 (1.4)
	Unknown	2 (2.8)
Height (cm)	n	59
	Mean	114
	SD	18.68
	Median	113
	Q1,Q3	98.4,129.0
	Min,Max	85.1,161.0
Body Weight (kg)	n	65
	Mean	21.9
	SD	11.13
	Median	18.5
	Q1,Q3	15.5,24.9
	Min,Max	10.7,81.5
Disease Status	Group 1: Primary refractory	19 (26.4)

{DANYELZA, naxitamab-gqgk}

	Statistic	Overall (N=72) [n(%)]
	Group 2: Second or greater CR or good partial remission with risk of relapse	23 (31.9)
	Group 3: Incomplete response to salvage therapy	24 (33.3)
	NED	5 (6.9)
	Progressive Disease	1 (1.4)
Age at diagnosis (years)	n	72
	Mean	3.8
	SD	2.73
	Median	3.0
	Q1,Q3	2.0,6.0
	Min,Max	0, 12

Adequacy of the safety database:The Applicant's Position:

The evaluation of safety is based on data from four clinical trials and a retrospective study with data collected from subjects treated in a compassionate-use program and exposed to at least 1 dose of study treatment. Further details are provided in Section 8.2.

This population allows for an informed assessment of the safety profile of naxitamab in combination with GM-CSF for the treatment of high-risk refractory or relapsed neuroblastoma in bone and/or bone marrow.

The FDA's Assessment:

FDA's evaluation of safety is based primarily on the data from 117 unique patients enrolled in Trial 12-230 and 25 unique patients enrolled in Trial 201. Analyses of data from other studies were considered supportive.

Given the data collection in Trial 12-230 there are several limitations to the safety database. Comprehensive collection of Grade 1 – 2 AEs was not required beyond Cycle 2 in this study. In addition, action taken with the product in response to an adverse event was not captured in a

standard fashion. Dose discontinuations and modifications are described in the review to the extent possible based on analyses of the safety database and safety narratives provided.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted data sets and individual case narratives.

The FDA's Assessment:

See description of limitations of the database on the preceding page.

Categorization of Adverse Event

The Applicant's Position:

The safety evaluation of naxitamab in combination with GM-CSF included the following:

- Treatment-emergent adverse events (TEAEs), defined as any AE with onset date from the day of the first infusion of naxitamab up to and including 30 days after the last naxitamab infusion
- Serious TEAEs, including deaths
- TEAEs leading to treatment discontinuation
- AEs of special interest (AESIs)
- Immunogenicity
- Clinical laboratory results
- Vital signs
- Safety in special groups (by age, body weight, gender, race, prior anti-GD2 treatment, and ADA-status)

The Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 was used for coding of AEs in Trials 12-230, 201, 11-009, and 12-116. MedDRA Version 21.1 was used for coding of AEs in 2PR01. MedDRA Version 20.1 was used for coding of AEs for the ISS.

AEs were graded using the National Cancer Institute CTCAE (Version 4) in all trials.

{DANYELZA, naxitamab-gqgk}

The FDA's Assessment:

FDA agrees with the description of adverse event classification above.

Routine Clinical Tests

The Applicant's Position:

In Trials 201, 12-230, 11-009, and 12-116, routine clinical laboratory data were collected and evaluated as described in the protocols.

Under the 2PR01 retrospective study protocol, routine clinical laboratory data were not collected.

The summaries included all laboratory assessments collected no later than 30 days after end of naxitamab treatment.

The FDA's Assessment:

Routine clinical tests in Trial 12-230 included:

- Chemistry including liver function testing (before each cycle and ~3 days after the last dose of naxitamab for each cycle)
- Complete blood count on Day -4 prior to starting GM-CSF, and before GM-CSF on Days 1 – 5.
- ECG after dosing of naxitamab during Cycle 1 and then as clinically indicated
- Evaluation for anti-drug antibodies (ADA) before each cycle
- Tumor evaluation including bone marrow evaluation and imaging (CT, MRI, MIBG scan or PET scan) before cycle 2, after cycle 4, and approximately every 3 months for 18 months from first treatment
- Pain assessment and vital signs prior to and during infusion of naxitamab and prior to discharge from the day hospital

Routine clinical tests in Trial 201 included:

- Chemistry including liver function testing on Days 1, 3, and 5 of Cycle 1 and prior to each subsequent cycle.
- Complete blood count on Day -4 prior to starting GM-CSF, and before GM-CSF on Days 1, 3 and 5.
 - Note that per protocol, if Absolute Neutrophil Count (ANC) >20,000/mm³ or platelet count >500,000/mm³, GM-CSF was held until values fall below the abovementioned thresholds. CBC was repeated on sequential days for an

{DANYELZA, naxitamab-gqgk}

ANC >20,000/mm³ or platelet count >500,000/mm³.

- ECG during screening, before Cycles 2 and 4 and at the end of treatment
- Evaluation for ADA prior to infusion on Days 1, 3, and 5, in Cycle 1 and prior to naxitamab administration during subsequent cycles.
- Tumor evaluation including bone marrow evaluation and imaging (CT, MRI, MIBG scan or PET scan) approximately every 2 – 3 months with exact schedule as follows:
 - Bilateral bone marrow biopsies and aspirates performed Week 6 (post Cycle 2 (C2)).
 - For patients with CR or PR at Week 6 (post C2): repeat sampling Weeks 18 (+1 week), 30 (+1 week), 46 (±1 week), 62 (±1 week) and 78 (±1 week). The repeat sampling planned at Week 18 and 30 had to be scheduled with a minimum of 12 weeks since last sampling.
 - For patients with MR or SD at Week 6 (post C2): repeat sampling at Weeks 14 (post C4), 26 (+1 week), 38 (+1 week), 54 (±1 week), and 78 (±1 week). The repeat sampling planned at Weeks 26 and 38 had to be scheduled with a minimum of 12 weeks since last sampling.
- Pain assessment and vital signs prior to and during infusion of naxitamab and prior to discharge from the day hospital
 - Per protocol vital signs were assessed prior to pre-medication, prior to naxitamab infusion, 30 minutes after naxitamab infusion, prior to each narcotic dose, at completion of naxitamab infusion, at completion of flush, 15 minutes after completion of flush, and every hour while patient is recovering in clinic post-infusion.
 - Patients were required to be monitored for at least two hours after completion of treatment, or two hours after the last dose of IV narcotics were administered, whichever was latest.

8.2.4. Safety Results

Deaths

The Applicant's Position:

No deaths were reported during naxitamab treatment or in the 30-day period following the end of treatment.

The FDA's Assessment:

FDA agrees the with the Applicant's position and has no additional comments.

{DANYELZA, naxitamab-gqgk}

Serious Adverse EventsThe Applicant's Position:**Serious Adverse Events (SAEs)**

In Trial 12-230, the percentage of subjects reporting at least one SAE was 41.0%. SAEs reported in at least 5% of all SAF subjects included hypotension (11.1%), hypertension (10.3%), pyrexia (9.4%), and device-related infection (6.8%).

In Trial 201, the percentage of subjects reporting at least one SAE was 32.0%. SAEs reported in at least 5% of all subjects included anaphylactic reaction (12.0%) and pain (8.0%).

In 2PR01, the percentage of patients reporting at least one SAE was 32.7%. SAEs reported in at least 5% of all patients included angioedema (5.8%).

Treatment-related SAEs

Treatment-related SAEs reported for Trial 12-230 SAF subjects, Trial 201 subjects, and patients in 2PR01, is presented side-by-side in Table 8-24.

Treatment-related SAEs were reported for 29.1% of subjects in Trial 12-230 SAF. Treatment-related SAEs reported for 2 or more subjects included hypertension (10.3%), hypotension (7.7%), pyrexia (5.1%), pain (1.7%), pyrexia (1.7%), vomiting (1.7%), anaphylactic reaction (1.7%), and posterior reversible encephalopathy syndrome (PRES) (1.7%).

In Trial 201, treatment-related SAEs were reported for 20% of subjects. Treatment-related SAEs reported for 2 or more subjects included anaphylactic reaction (12%).

In 2PR01, 17.3% unique patients reported at least one treatment-related SAE. Treatment-related SAEs reported for 2 or more subjects included bronchospasm (3.8%) and angioedema (5.8%).

Table 8-24 Summary of Treatment-related^a SAEs Reported for Trial 12-230, Trial 201, and Retrospective Trial 2PR01 (SAF)

	Trial 12-230^b	Trial 201	2PR01^c
System Organ Class/ Preferred Term	All Subjects (N=117) [n(%) events]	All Subjects (N=25) [n(%)#events]	All Groups (N=52) [n(%)#events]
Number of subjects with at least one related SAE	34 (29.1), 49	5 (20.0), 6	9 (17.3), 14
Vascular disorders	21 (17.9), 22	0	0
Hypertension	12 (10.3), 13	0	0

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	Trial 12-230 ^b	Trial 201	2PR01 ^c
	All Subjects (N=117) [n(%) events]	All Subjects (N=25) [n(%)#events]	All Groups (N=52) [n(%)#events]
Hypotension	9 (7.7), 9	0	0
General disorders and administration site conditions	8 (6.8), 8	1 (4.0), 1	0
Pyrexia	6 (5.1), 6	1 (4.0), 1	0
Pain	2 (1.7), 2	0	0
Immune system disorders	3 (2.6), 3	3 (12.0), 4	2 (3.8), 2
Anaphylactic reaction	2 (1.7), 2	3 (12.0), 4	1 (1.9), 1
Hypersensitivity	1 (0.9), 1	0	0
Anaphylactic shock	0	0	1 (1.9), 1
Gastrointestinal disorders	2 (1.7), 3	0	0
Vomiting	2 (1.7), 2	0	0
Nausea	1 (0.9), 1	0	0
Nervous system disorders	2 (1.7), 2	0	1 (1.9), 1
Posterior reversible encephalopathy syndrome	2 (1.7), 2	0	0
Neuralgia	0	0	1 (1.9), 1
Renal and urinary disorders	2 (1.7), 2	0	1 (1.9), 1
Acute kidney injury	1 (0.9), 1	0	0
Urinary retention	1 (0.9), 1	0	0
Renal failure	0	0	1 (1.9), 1
Respiratory, thoracic and mediastinal disorders	2 (1.7), 3	1 (4.0), 1	5 (9.6), 7
Hypoxia	1 (0.9), 1	0	0
Respiratory distress	1 (0.9), 1	0	0
Wheezing	1 (0.9), 1	0	0
Respiratory depression	0	1 (4.0), 1	0
Bronchospasm	0	0	2 (3.8), 2
Laryngeal oedema	0	0	1 (1.9), 1
Respiratory tract oedema	0	0	1 (1.9), 2
Stridor	0	0	1 (1.9), 2
Skin and subcutaneous tissue disorders	2 (1.7), 2	0	3 (5.8), 3
Angioedema	1 (0.9), 1	0	3 (5.8), 3
Rash maculo-papular	1 (0.9), 1	0	0
Blood and lymphatic system disorders	1 (0.9), 1	0	0
Febrile neutropenia	1 (0.9), 1	0	0
Investigations	1 (0.9), 1	0	0
Neutrophil count decreased	1 (0.9), 1	0	0
Musculoskeletal and connective tissue disorders	1 (0.9), 1	0	0
Bone pain	1 (0.9), 1	0	0
Psychiatric disorders	1 (0.9), 1	0	0
Mental status changes	1 (0.9), 1	0	0

SAE = serious adverse event.

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

{DANYELZA, naxitamab-gqgk}

a: SAEs determined to be related to naxitamab by the investigator are shown for Trial 201 and 2PR01. SAEs determined to be treatment related by the investigator are shown for Trial 12-230; Y-mAbs' review of the SAE narratives for Trial 12-230 determined that three of the SAEs above were related to GM-CSF: one SAE of hypersensitivity for one subject, one SAE of neutrophil count decreased for one subject, and one SAE of bone pain for one subject.

b: Subjects are counted only once in each column for which they have an enrollment, and only AEs associated with the enrollment are presented.

c: Patients are counted only once, even though some patients had multiple enrollments.

The FDA's Assessment:

FDA performed an analysis of the incidence of SAEs in Trials 12-230 and 201, and performed a selective review of SAEs in Trial 11-009, 12-115 and 2PR01. FDA did not agree with the presentation of safety data noted above given the inclusion of only SAEs that were assessed as related by the investigator and requested a revised table including all treatment-emergent SAEs. Table 8-25 was provided by the Applicant and the data were confirmed by FDA.

Table 8-25: Summary of Serious Treatment Emergent Adverse Events Reported in at Least 2 Subjects by System Organ Class and Preferred Term Corresponding Serious, Treatment-Related Adverse Events Trial 12-230 Phase 1 and 2 Subjects with Dose of 3mg/kg (Safety Analysis Set) (Applicant's Analysis)

System Organ Class/ Preferred Term	All SAEs (N=72) [n(%)]	All Related SAEs (N=72) [n(%)]
Subjects with at least one serious TEAE	29 (40.3)	20 (27.8)
Vascular disorders	17 (23.6)	15 (20.8)
Hypertension	10 (13.9)	10 (13.9)
Hypotension	8 (11.1)	5 (6.9)
General disorders and	9 (12.5)	4 (5.6)
Pyrexia	6 (8.3)	2 (2.8)
Pain	3 (4.2)	2 (2.8)
Infections and infestations	8 (11.1)	0
Device related infection	3 (4.2)	0
Staphylococcal infection	2 (2.8)	0
Gastrointestinal disorders	6 (8.3)	2 (2.8)

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	All SAEs (N=72) [n(%)]	All Related SAEs (N=72) [n(%)]
Vomiting	3 (4.2)	2 (2.8)
Abdominal pain	2 (2.8)	0
Respiratory, thoracic and	5 (6.9)	2 (2.8)
Hypoxia	3 (4.2)	1 (1.4)
Apnea	2 (2.8)	0
Nervous system disorders	4 (5.6)	2 (2.8)
Posterior reversible encephalopathy syndrome	2 (2.8)	2 (2.8)

Note: Subjects could enroll multiple times and possibly in both phases (i.e., enrollment in Phase 1 and 2 or twice in Phase 2). N represents unique subjects.

Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are number of unique subjects who experienced at least one serious AE in that SOC or PT. Subjects who experienced more than one SAE in a given SOC or PT were counted only once for that particular SOC or PT.

Note: Enrollment cut off date for subject population is 15Jan2018. Data cutoff is 15May2018 for efficacy and 17Dec2018 for safety.

Date: 10JUL2020

Data Source: ADAE.sas7bdat, ADSL.sas7bdat

Program Source: TRFI23_2c.sas

FDA's analysis of SAEs in patients receiving the RP2D of naxitamab in Trial 12-230 also included patients who experienced mental status changes (2.8%), urinary retention (1.4%), and platelet count decreased (2.8%); According to FDA's analysis, 6.9% of patients had SAEs of pyrexia and 2.8% had pain, which slightly differ from the numbers presented above. Table 8-26 provides an overview of SAEs in patients treated at all dose levels in Trial 12-230, and the entire safety population of Trial 201 and Trial 2PR01. Note that FDA did not confirm incidences for Trial 2PR01.

{DANYELZA, naxitamab-gqgk}

Table 8-26: Summary of SAEs and Treatment-related SAEs Reported for Trial 12-230 Subjects, Trial 201 Subjects, and Retrospective Study 2PR01 Patients (Applicant's Analysis)

System Organ Class/ Preferred Term	Trial 12-230 ^a All Subjects (N=117)		Trial 201 All Subjects (N=25)		2PR01 ^b All Groups (N=52)	
	SAEs	Related SAEs	SAEs	Related SAEs	SAEs	Related SAEs
	[n(%)]	[n(%)]	[n(%)]	[n(%)]	[n(%)]	[n(%)]
Number of subjects with at least one SAE	48 (41.0)	34 (29.1)	8 (32.0)	5 (20.0)	17 (32.7)	9 (17.3)
Vascular disorders	24 (20.5)	21 (17.9)	0	0	1 (1.9)	0
Hypotension	13 (11.1)	9 (7.7)	0	0	0	0
Hypertension	12 (10.3)	12 (10.3)	0	0	0	0
Hypovolaemic shock	0	0	0	0	1 (1.9)	0
Infections and infestations	15 (12.8)	0	2 (8.0)	0	3 (5.8)	0
Device related infection	8 (6.8)	0	1 (4.0)	0	2 (3.8)	0
Staphylococcal infection	3 (2.6)	0	0	0	0	0
Bacterial infection	1 (0.9)	0	0	0	0	0
Haemophilus infection	1 (0.9)	0	0	0	0	0
Klebsiella infection	1 (0.9)	0	0	0	0	0
Parainfluenzae virus infection	1 (0.9)	0	0	0	0	0
Pneumonia	1 (0.9)	0	0	0	1 (1.9)	0
Sepsis	1 (0.9)	0	0	0	0	0
Influenza	0	0	1 (4.0)	0	0	0
General disorders and administration site conditions	14 (12.0)	8 (6.8)	3 (12.0)	1 (4.0)	2 (3.8)	0
Pyrexia	11 (9.4)	6 (5.1)	1 (4.0)	1 (4.0)	1 (1.9)	0
Pain	3 (2.6)	2 (1.7)	2 (8.0)	0	1 (1.9)	0
Gastrointestinal disorders	8 (6.8)	2 (1.7)	0	0	1 (1.9)	0
Abdominal pain	3 (2.6)	0	0	0	0	0
Vomiting	3 (2.6)	2 (1.7)	0	0	0	0
Colitis	1 (0.9)	0	0	0	0	0
Diarrhoea	1 (0.9)	0	0	0	0	0
Haemorrhoids	1 (0.9)	0	0	0	0	0
Nausea	1 (0.9)	1 (0.9)	0	0	0	0
Intestinal obstruction	0	0	0	0	1 (1.9)	0
Metabolism and nutrition disorders	6 (5.1)	0	0	0	0	0
Hypokalaemia	2 (1.7)	0	0	0	0	0
Acidosis	1 (0.9)	0	0	0	0	0
Decreased appetite	1 (0.9)	0	0	0	0	0
Dehydration	1 (0.9)	0	0	0	0	0
Hypocalcaemia	1 (0.9)	0	0	0	0	0
Hyponatraemia	1 (0.9)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	6 (5.1)	2 (1.7)	1 (4.0)	1 (4.0)	6 (11.5)	5 (9.6)

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

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	Trial 12-230 ^a		Trial 201		2PR01 ^b	
	All Subjects		All Subjects		All Groups	
	(N=117)		(N=25)		(N=52)	
	SAEs	Related SAEs	SAEs	Related SAEs	SAEs	Related SAEs
	[n(%)]	[n(%)]	[n(%)]	[n(%)]	[n(%)]	[n(%)]
Hypoxia	4 (3.4)	1 (0.9)	0	0	0	0
Apnoea	2 (1.7)	0	0	0	1 (1.9)	0
Cough	1 (0.9)	0	0	0	0	0
Dyspnoea	1 (0.9)	0	0	0	0	0
Hypopnoea	1 (0.9)	0	0	0	0	0
Respiratory distress	1 (0.9)	1 (0.9)	0	0	0	0
Wheezing	1 (0.9)	1 (0.9)	0	0	0	0
Respiratory depression	0	0	1 (4.0)	1 (4.0)	0	0
Bronchospasm	0	0	0	0	2 (3.8)	2 (3.8)
Laryngeal oedema	0	0	0	0	1 (1.9)	1 (1.9)
Respiratory tract oedema	0	0	0	0	1 (1.9)	1 (1.9)
Stridor	0	0	0	0	1 (1.9)	1 (1.9)
Investigations	4 (3.4)	1 (0.9)	0	0	0	0
Platelet count decreased	2 (1.7)	0	0	0	0	0
Neutrophil count decreased	1 (0.9)	1 (0.9)	0	0	0	0
Urine output decreased	1 (0.9)	0	0	0	0	0
Nervous system disorders	4 (3.4)	2 (1.7)	0	0	2 (3.8)	1 (1.9)
Posterior reversible encephalopathy	2 (1.7)	2 (1.7)	0	0	0	0
Aphasia	1 (0.9)	0	0	0	0	0
Headache	1 (0.9)	0	0	0	0	0
Haemorrhage intracranial	0	0	0	0	1 (1.9)	0
Neuralgia	0	0	0	0	1 (1.9)	1 (1.9)
Immune system disorders	3 (2.6)	3 (2.6)	3 (12.0)	3 (12.0)	2 (3.8)	2 (3.8)
Anaphylactic reaction	2 (1.7)	2 (1.7)	3 (12.0)	3 (12.0)	1 (1.9)	1 (1.9)
Hypersensitivity	1 (0.9)	1 (0.9)	0	0	0	0
Anaphylactic shock	0	0	0	0	1 (1.9)	1 (1.9)
Psychiatric disorders	3 (2.6)	1 (0.9)	0	0	0	0
Mental status changes	3 (2.6)	1 (0.9)	0	0	0	0
Renal and urinary disorders	3 (2.6)	2 (1.7)	0	0	2 (3.8)	1 (1.9)
Urinary retention	2 (1.7)	1 (0.9)	0	0	1 (1.9)	0
Acute kidney injury	1 (0.9)	1 (0.9)	0	0	0	0
Renal failure	0	0	0	0	1 (1.9)	1 (1.9)
Cardiac disorders	2 (1.7)	0	0	0	0	0
Cardiac arrest	1 (0.9)	0	0	0	0	0
Sinus tachycardia	1 (0.9)	0	0	0	0	0
Skin and subcutaneous tissue disorders	2 (1.7)	2 (1.7)	0	0	3 (5.8)	3 (5.8)
Angioedema	1 (0.9)	1 (0.9)	0	0	3 (5.8)	3 (5.8)
Rash maculo-papular	1 (0.9)	1 (0.9)	0	0	0	0
Blood and lymphatic system disorders	1 (0.9)	1 (0.9)	0	0	0	0

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	Trial 12-230 ^a		Trial 201		2PR01 ^b	
	All Subjects		All Subjects		All Groups	
	(N=117)		(N=25)		(N=52)	
	SAEs	Related SAEs	SAEs	Related SAEs	SAEs	Related SAEs
	[n(%)]	[n(%)]	[n(%)]	[n(%)]	[n(%)]	[n(%)]
Febrile neutropenia	1 (0.9)	1 (0.9)	0	0	0	0
Musculoskeletal and connective tissue	1 (0.9)	1 (0.9)	0	0	1 (1.9)	0
Bone pain	1 (0.9)	1 (0.9)	0	0	0	0
Back pain	0	0	0	0	1 (1.9)	0
Neoplasms benign, malignant and	0	0	0	0	1 (1.9)	0
Tumour haemorrhage	0	0	0	0	1 (1.9)	0

Source: [Trial 12-230](#) Table 14.3.1.9.1, Table 14.3.1.11.1, Appendix 16.2.7.1; [Trial 201](#) Table 14.3.1.4, Table 14.3.1.5.2, and Appendix 16.2.7.1.1; [Retrospective Study 2PR01](#) Table 14.3.1.8, Table 14.3.1.23, Appendix 16.2.7.1. SAE = serious adverse event.

„Subjects are counted only once in each column for which they have an enrollment and only SAEs associated with the enrollment are presented.

„Subjects are counted only once even though some subjects had multiple enrollments.

All SAE narratives for Trial 12-230 and Trial 201 were reviewed. Several SAEs which occurred in more than one patient are presented in Table 8-27. Please see section 8.2.5 for a discussion of Adverse Events of Special Interest (AESI) including infusion-related reactions (IRRs), and events of neurotoxicity including posterior reversible encephalopathy syndrome (PRES)/ reversible posterior leukoencephalopathy syndrome (RPLS).

Table 8-27: Selected Serious Adverse Event Narratives from Trials 12-203 and 201

Preferred Term/ Patient ID	Narrative and Reviewer Comments
Mental Status changes	
Patient (b) (6)	This is a 10-year-old male with stage 4 neuroblastoma enrolled in Study 12-230 who experienced mental status changes two days after completion of 3rd cycle of naxitamab. The patient woke up crying, then fell back asleep and was unarousable according to his mother. He alternated between being unresponsive and being awake and screaming. Upon evaluations the potential etiology was considered to be potentially related to use of cannabidiol or seizures (although no seizure activity was observed on EEG).

{DANYELZA, naxitamab-gqgk}

Preferred Term/ Patient ID	Narrative and Reviewer Comments
	He experienced mental status changes after Cycle 4 as well. Again, two days after receipt of naxitamab, the patient was lethargic and difficult to arouse. Upon arrival to urgent care, the patient was 'dusky and unresponsive' and was placed on BiPap. He was treated for UTI, evaluated for seizures and for meningitis/encephalitis. A workup for infectious causes of meningitis and encephalitis was negative. <i>Reviewer comment: The pattern of two episodes of neurologic changes after receipt of naxitamab is concerning. Of note, this patient had also received the anti-GD2 antibody 8H9 at MSKCC and dinutuximab via a COG protocol. In addition, in response to an information request regarding a subsequent event of cardiac arrest (described later in this section), the investigator stated that this patient had baseline neurologic deficits related to his disease, confounding assessment of this event. Serious neurologic sequelae were not reported for subsequent cycles of naxitamab.</i>
Patient (b) (6)	This patient enrolled in Study 12-230 (the same patient described in the narrative for (b) (6) above) experienced concomitant Grade 4 hyponatremia, which is the likely etiology of the altered mental status .
Patient (b) (6)	This is a 24-year-old male with high-risk neuroblastoma enrolled in Study 12-230 who experienced Grade 3 aphasia following his 7th cycle of naxitamab. Three days following administration of naxitamab he reported difficulty speaking, headache and photophobia; he also reported difficulty spelling out words and texting, and had 2 episodes of emesis. He was evaluated for PRES and treated for hypertension. MRI did not demonstrate PRES and he was treated with gabapentin for pain. The event was considered not related to protocol therapy. <i>Reviewer comment: The Applicant assessed the event as not related to naxitamab but an alternative etiology is not presented.</i>
Patient (b) (6)	This is a 6-year-old with high risk neuroblastoma enrolled in Study 12-230 who developed hypotension and mental status changes after receiving one dose of naxitamab. At the end of infusion she became acutely rigid, postured and was unresponsive and dusky. She was administered Narcan out of concern for hydromorphone overdose and Ativan out of concern for seizure activity with some improvement in responsiveness after medication, and was given fluid due to hypotension (87/49). Workup including brain imaging did

{DANYELZA, naxitamab-gqgk}

Preferred Term/ Patient ID	Narrative and Reviewer Comments
	not reveal intracranial disease or bleeding. Both hypotension and altered mental status were considered related to protocol therapy. <i>Reviewer comment: This event appears to be an infusion reaction with hypotension; the altered mental status may be secondary to pain medication or seizure activity given improvement with treatment with Narcan and lorazepam.</i>
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)/ Posterior Reversible Encephalopathy Syndrome (PRES)	
Patient (b) (6)	This is a 7-year-old with Stage 4 neuroblastoma who experienced Grade 3 PRES two days following completion of naxitamab administration during Cycle 1 of therapy on Study 12-203. One day after naxitamab administration he developed nausea, emesis, headache, and transient bilateral vision loss which was self-resolved. Two days after naxitamab administration, he presented to a local hospital and was found to be hypertensive (150/100). He was treated with antihypertensive medication, but developed a generalized tonic-clonic seizure and was admitted to the pediatric intensive care unit (PICU). He was intubated and EEG demonstrated subclinical status epilepticus for approximately 2 hours. An MRI obtained the next day demonstrated posterior reversible leukoencephalopathy syndrome (RPLS). The patient subsequently received one additional cycle of naxitamab before being removed due to ADA.
Patient (b) (6)	This is a 5 year old female with Stage 4 neuroblastoma who experienced Grade 3 PRES following Cycle 1 of naxitamab on Study 12-203. Seven days after completing naxitamab she presented to her local hospital with nausea, headaches, abdominal pain, and was found to be hypertensive with altered mental status and seizure activity. She was intubated, treated with antiepileptics and antihypertensive medications. MRI confirmed RPLS/PRES. The patient discontinued naxitamab due to the event.
Apnea	
Patient (b) (6)	This is a 10-year-old male with Stage 4 neuroblastoma enrolled in Study 12-230 who experienced Grade 3 apnea and hypoxia during his second dose of naxitamab. Episodes of desaturation were self-resolving and occurred while awake and asleep. He was treated with antibiotics based on new right lower lobe opacity on chest x-ray and given oxygen by nasal cannula. Sleep study

{DANYELZA, naxitamab-gqgk}

Preferred Term/ Patient ID	Narrative and Reviewer Comments
	demonstrated central hypopnea requiring BiPAP while asleep. Patient continued BiPAP overnight while on study.
Patient (b) (6)	This is an 11-year-old male with Stage 4 neuroblastoma enrolled in Study 12-230 who experienced Grade 3 apnea and mental status changes following Cycle 1 of naxitamab. He presented the day following completion of naxitamab administration with continued pain as well as hypertension, and was treated for pain and hypertension. Four days after completion of naxitamab he returned to clinic with generalized pain and abdominal pain. His mother also reported that he had been unresponsive for 3 - 4 seconds when she tried to wake him. Upon arrival he had delayed capillary refill and hypotension (60s/30s). During this hospitalization he had brief episodes of apnea. He was treated presumptively for sepsis and evaluated for seizures. The neurologic events were assessed as not related to protocol therapy. <i>Reviewer comment: The patient's apparent episodes of apnea maybe related to use of morphine for pain.</i>
Acute Kidney Injury	
Patient (b) (6)	This is a 15-year-old female with Stage 4 neuroblastoma enrolled in Study 12-230 who experienced Grade 4 acute kidney injury following Cycle 1 of treatment with naxitamab. Two days after completion of the last dose of Cycle 1 of naxitamab, the patient experienced nausea and vomiting and was seen in urgent care. Two days later she was evaluated for constipation. Laboratory studies demonstrated a Grade 3 creatinine elevation (4.5 mg/dl; normal 0.6-1.3 mg/dl); her BUN was also increased (40 mg/dl; normal range 6-20 mg/dl). She began dialysis for acute kidney injury. During the admission, she had a kidney biopsy which revealed a mild to moderate diffuse, acute tubular injury, fairly diffuse active interstitial inflammation, and mild glomerulomegaly with increased extracellular matrix. The patient's kidney injury appeared to completely recover by the time of follow-up one month later. The event was considered a dose-limiting toxicity and the patient was removed from protocol therapy. (dose: 2.6 mg/kg/day) <i>Reviewer comment: The preceding history of nausea and vomiting could indicate that the renal injury is largely pre-renal. Severe volume depletion can precipitate acute tubular necrosis. The interstitial inflammation seen on kidney biopsy could also indicate acute interstitial nephritis, which would most likely be drug-related. The patient recovered following dialysis but as no further naxitamab was given, recovery does not provide additional insight</i>

{DANYELZA, naxitamab-gqgk}

Preferred Term/ Patient ID	Narrative and Reviewer Comments
	<i>into the etiology of the kidney injury. This reviewer agrees with the sponsor's assessment that the kidney injury was possibly related to naxitamab.</i>
Respiratory symptoms	
(b) (6)	This is a 5-year-old boy diagnosed with Stage 4 neuroblastoma enrolled in Study 12-230 who developed Grade 2 respiratory distress during Cycle 6 of naxitamab. He received blow-by oxygen and nebulizers during administration of doses 1 and 2 of naxitamab and was evaluated in an urgent care center the day following Dose 2 due to wheezing and oxygen desaturation with visible work of breathing. He received nebulizers, hydroxyzine, and Singulair. A respiratory viral panel was negative. His 3rd dose of naxitamab for that cycle was held, and he was treated with albuterol, Singulair and Claritin. He was admitted overnight and the event was reported as resolved the next day. He received the subsequent cycle of naxitamab prior to discontinuing due to completion of therapy (the patient demonstrated a complete response). <i>Reviewer comment: The narrative demonstrates that respiratory supportive care was needed during infusion and subsequently recurred after infusion. The need for respiratory support during infusion suggests that this was an infusion reaction.</i>
Patient (b) (6)	This is a 4-year-old year-old with Stage 4 neuroblastoma enrolled in Study 12-230 who developed Grade 3 pneumonia, 12 days after his 1st dose of naxitamab. Later, during his second cycle he presented again with wheezing prior to Dose 2 of naxitamab, and developed a fever post-dose with hypoxia and stridor. He was treated with racemic epinephrine, albuterol, and started on antibiotics for left lower lobe opacity. <i>Reviewer comment: The event of pneumonia does not appear to be related to naxitamab, but the respiratory distress during the patient's second cycle likely represents a component of bronchospasm related to naxitamab on top of underlying pneumonia.</i>
Patient (b) (6)	This is a 9-year-old with Stage 4 neuroblastoma enrolled on Trial 12-230 who developed Grade 3 hypoxia during his second dose of Cycle 2

{DANYELZA, naxitamab-gqgk}

Preferred Term/ Patient ID	Narrative and Reviewer Comments
	of naxitamab. He had intermittent hypoxia down to 75% but the episodes were transient and would return to >95% without O ₂ . Pt was Rhinovirus positive and received guaifenesin/codeine and albuterol for cough. He later completed his second cycle without incident.
Hypotension	
Patient (b) (6)	This is a 21-year-old with Stage 4 neuroblastoma treated on Trial 12-230 who developed Grade 3 hypotension following the first dose of his second cycle of naxitamab. He was admitted for management of hypotension and briefly required dopamine for blood pressure support.
Patient (b) (6)	Gr 2 -8 year old boy diagnosed with Stage 4 neuroblastoma. During his first naxitamab infusion, the patient became diaphoretic, hypoxic, and hypotensive with a blood pressure (BP) of 50/30's mm Hg (Grade 2). He was also noted to have decreased peripheral perfusion and hives. He was given a dose of Narcan without improvement, a total of 60 ml/kg of normal saline boluses with transient increase in blood pressure, 2 EpiPen Jr injections, and 2 racemic epinephrine nebulizers for mild stridor. He received the remaining two doses of naxitamab of the cycle.
Patient (b) (6)	This is a 10-year-old male with Stage 4 neuroblastoma enrolled on Trial 12-230 who developed Grade 2 hypotension during his first infusion of Cycle 5 of naxitamab, requiring two normal saline boluses. He subsequently (after the infusion) developed fever and rigors and was treated with antibiotics. He was monitored inpatient overnight and was discharged the following day.
Patient (b) (6)	This patient enrolled on Trial 12-230 developed fever 3 hours after infusion of naxitamab and blood cultures grew out coagulase negative staphylococcus. He became tachycardic and hypotensive and was admitted to the PICU.

{DANYELZA, naxitamab-gqgk}

Preferred Term/ Patient ID	Narrative and Reviewer Comments
	<i>Reviewer note: Although fever and hypotension are commonly seen as part of infusion reactions, given the positive blood culture this case of hypotension appears to be related to sepsis.</i>
Patient (b) (6)	This is a 5-year old with Stage 4 neuroblastoma treated on protocol 12-230 who experience Grade 1 hypotension (serious due to hospitalization). She remained admitted following administration of her first dose of naxitamab (second cycle) through second dose of naxitamab for BP monitoring given the patients' history of PRES with the first cycle of naxitamab. The hospitalization was extended as she was intermittently febrile and hypotensive.
Patient (b) (6)	This is a 5-year-old with Stage 4 neuroblastoma treated on Study 12-230 who experienced fever, tachycardia and hypotension the day following his 3rd dose of cycle 7 of naxitamab. Blood cultures were positive (grew gram positive bacteria in pairs and chains within 12 hours).
Patient (b) (6)	This is a 12-year-old with Stage 4 neuroblastoma treated on Study 12-230 who. The day following her 3rd dose of the 6th cycle of naxitamab, she developed fever and was evaluated in a local ER. She subsequently developed hypotension and was admitted to the PICU. Blood cultures grew Staphylococcus aureus. <i>Reviewer note: Although fever and hypotension are commonly seen as part of infusion reactions, given the positive blood culture this case of hypotension appears to be related to sepsis.</i>
Patient (b) (6)	This is an 8-year-old boy with Stage 4 neuroblastoma who developed Grade 2 hypotension following first dose of the 8th cycle of naxitamab, patient developed hypotension requiring one NS bolus. The patient was discontinued from protocol therapy per parental decision; the 8th cycle was due to be his last cycle of naxitamab.
Patient (b) (6)	This is a 6-year-old with high risk neuroblastoma who developed hypotension and mental status changes after receiving one dose of naxitamab. At the end of infusion she became acutely rigid, postured and was unresponsive and dusky. She was administered Narcan out of

{DANYELZA, naxitamab-gqgk}

Preferred Term/ Patient ID	Narrative and Reviewer Comments
	concern for hydromorphone overdose and Ativan out of concern for seizure activity with some improvement in responsiveness after medication, and was given fluid due to hypotension (87/49). Workup including brain imaging did not reveal intracranial disease or bleeding. Both hypotension and altered mental status were considered related to protocol therapy.
Patient (b) (6)	This is a 5-year-old with Stage 4 neuroblastoma who experienced Grade 3 hypotension following first dose of third cycle of naxitamab. She was treated with fluid resuscitation, Narcan, and empiric antibiotics; she had a single fever (38.1) upon transfer to the PICU. She received the second dose of cycle 3 on schedule and again became hypotensive. She was treated with metronidazole for <i>C. difficile</i> positive stool culture, as well as hydrocortisone and broad spectrum antibiotics. The patient did not receive the third dose of naxitamab but did receive a fourth cycle prior to being removed from therapy per parental decision to discontinue.
Patient (b) (6)	This is a 3 year old female diagnosed with Stage 4 neuroblastoma who experienced Grade 3 hypoxia and hypotension immediately following the first dose of cycle 3 of naxitamab. She became hypotensive, pale, diaphoretic and had altered mental status. She received fluid resuscitation (four 20 cc/kg normal saline boluses), epinephrine, and oxygen; she was briefly given respiratory support with a bag-valve-mask (60-90 seconds) and was admitted overnight for monitoring in the PICU. She went on to receive subsequent cycles of naxitamab.
Patient (b) (6)	This is a 4-year-old female with Stage 4 neuroblastoma who experienced Grade 3 hypotension at the end of her first dose of naxitamab. She was given Narcan, epinephrine, and four 20 cc/kg boluses of normal saline. She was admitted to the PICU and treated empirically for sepsis, but was discharged the following day. She went on to complete Cycles 1 and 2 of naxitamab.
Patient (b) (6)	This is 6 year old male with stage 4 neuroblastoma who experienced hypotension during anesthesia induction for surgery on his right femur approximately 3 weeks after completing his fifth cycle of naxitamab.

{DANYELZA, naxitamab-gqgk}

Preferred Term/ Patient ID	Narrative and Reviewer Comments
Other	
Patient (b) (6)	This is a 10-year-old male with Stage 4 neuroblastoma enrolled in Study 12-230 who experienced a cardiac arrest following Cycle 6 dose 1 of naxitamab. Following completion of the infusion and after his last narcotic rescue (approximately 1.5 hours from the time of naxitamab infusion completion and hydromorphone completion), patient fainted and became cyanotic and unresponsive. He received two minutes of CPR and IM epinephrine. He was monitored overnight in the PICU. The event was assessed as not related to protocol therapy. <i>Reviewer note: In response to an information request the investigator provided rationale for stating the event was not related to naxitamab. This patient had received >5 years of aggressive multimodality therapy including intrathecal and radiation treatments for three relapses in the brain, with residual central and peripheral neurological defects including central and obstructive sleep apnea. He often experienced periods of unresponsiveness apparently unrelated to any oncologic treatment which necessitated emergency transport.</i> <i>Given the clinical history of this patient, this reviewer agrees that this event may be unrelated to naxitamab; however, as cardiac arrest and sudden death have been rarely reported following administration of dinutuximab, the reviewer feels a contribution of naxitamab cannot be entirely excluded.</i>

Source: FDA primary clinical review, CSRs for Trial 12-230 and 201

One additional serious adverse event in a patient receiving naxitamab was submitted to IND 132793 but was not included in the BLA safety population. This patient received naxitamab in combination with GM-CSF according to the MSK study entitled “16-1643: Naxitamab (Hu3F8) /GM-CSF Immunotherapy Plus Isotretinoin for Consolidation of First Remission of Patients with High-Risk Neuroblastoma: A Phase II Study.” The narrative provided in the IND safety report is summarized below.

This is a 13 year-old male with Stage 4 high-risk neuroblastoma initially treated with chemotherapy and surgery. He was then treated with irinotecan and temozolomide in combination with dinutuximab, but he discontinued dinutuximab due to severe

{DANYELZA, naxitamab-gqgk}

neuropathic pain which did not resolve prior to the following cycle. He was later consented to a single patient use protocol with the same regimen as MSK study 16-1643, with doses of naxitamab and GM-CSF identical to those used in Trial 12-230. The patient experienced severe neuropathic pain of the lower extremity after the first two doses of his first cycle of naxitamab. Following the third dose, he experienced urinary retention, lower extremity weakness with inability to walk or bear weight, and severe intermittent back pain. Workup demonstrated T2 hyperintensity of the spinal cord at all levels, and examination demonstrated bilateral lower extremity weakness and decreased sensation, which improved after treatment with IV methylprednisolone. The subsequent day he required increasing respiratory support and heart failure, and he was treated for multifocal pneumonia; he also developed acute renal insufficiency. Naxitamab was withdrawn as a result of the event, and the event of transverse myelitis was assessed as possibly related to naxitamab by the Applicant.

Reviewer comment: Given the mechanism of action of naxitamab, and the observation of transverse myelitis in patients receiving other anti-GD2 antibodies, the event seems likely to be related to naxitamab. The additional adverse events of heart failure, pneumonia, and renal insufficiency are not well described in the narrative, which indicates “despite several attempts, no further information provided.” The Applicant has included transverse myelitis as a warning in Section 5 of the label, and this reviewer agrees that it should be included.

Additional serious adverse event narratives were provided as part of the 120-day safety update, as described in Table 8-28 below. There were no additional SAEs from the safety population of Trial 12-230 (enrolled by 01/15/2018 with events occurring by 5/15/2018), but additional SAEs were provided for patients enrolled after 01/15/2018 and with events occurring up to 11/27/2019. These events are summarized in Table 8-29, adapted from the sponsor’s submission below.

Table 8-28: Serious Adverse Events in Trial 201: 120-day Safety Update

Subject ID	Preferred Term
(b) (6) / Event 2	Hypomagnesaemia
	Generalized tonic-clonic seizure
	Device related infection
	Device related infection
	Hypotension
	Laryngeal edema
/ Event 1	Hypotension

{DANYELZA, naxitamab-gqgk}

Subject ID	Preferred Term
(b) (6) / Event 2	Febrile neutropenia

Source: 120-day update submitted 7/30/2020

The event of generalized tonic-clonic seizure occurred in a patient with a newly-diagnosed brain metastasis. The event of hypomagnesemia appears to have been considered serious given the patient's hospitalization, though hospitalization appears to have been driven by concomitant fever and treatment with broad-spectrum antibiotics.

Table 8-29: Serious Adverse Events in Trial 12-230: 120-Day Safety Update

Subject ID	Preferred Term
(b) (6)	Event 1 Hypotension
	Event 2 Hypotension
	Event 1 Vision blurred; Hypertension
	Event 1 Hypotension; Hyperglycemia
	Event 1 Lung infection
	Event 1 Anaphylactic reaction
	Event 1 Hypertension
	Event 1 Hypertension
	Event 1 Hypertension; Blood bilirubin increased
	Event 2 Hypertension
	Event 3 Hypertension; Pain
	Event 1 Pain
	Event 2 Hypotension
	Event 3 Pain
	Event 4 Pain
	Event 1 Upper respiratory infection; Pyrexia
	Event 1 Hypotension
	Event 1 Dehydration; Vascular access complication; Alanine aminotransferase increased; Aspartate aminotransferase increased
	Event 1 Enterococcal infection
	Event 1 Diarrhea; Vomiting
	Event 2 Vomiting
	Event 3 Hypertension
	Event 1 Vomiting
	Event 2 Hypertension
	Event 1 Abdominal pain; Blood bilirubin increased
	Event 1 Device related infection
	Event 1 Anaphylactic reaction; Bradycardia

{DANYELZA, naxitamab-gqgk}

(b) (6)	Event 1	Hypertension
	Event 1	Device related infection
	Event 1	Urinary tract infection
	Event 2	Urinary tract infection
	Event 1	Device related infection

Source: 120-day update submitted 7/30/2020

The narratives submitted in the 120-day safety update did not suggest new safety signals compared to the data included in the original BLA submission.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Discontinuations due to AEs were few. In Trial 12-230 Phase 1, 4 subjects discontinued due to dose-limiting toxicity (DLT): anaphylactic reaction, acute kidney injury, altered mental status, and hypertension; and 3 subjects discontinued due to AEs: anaphylactic reaction, angioedema, and hypotension. In Trial 12-230 Phase 2, three subjects discontinued due to hypertension, one subject due to PRES, and one subject due to excessive toxicity, where no specific AEs, but a number of nonserious AEs could be linked to the discontinuation. In Trial 201, two subjects discontinued due to anaphylactic reaction, and one subject due to respiratory depression. In 2PR01, four patients discontinued due to AEs: anaphylactic shock, neuralgia, apnoea (nonserious), and tumor haemorrhage (not related to naxitamab).

The FDA's Assessment:

FDA agrees with the description of discontinuations due to adverse events in Trial 201.

Action taken with naxitamab in response to specific adverse events was not reliably captured during Trial 12-230 and this information was not included as a standard variable in the adverse event dataset. The Applicant conducted a review of narratives and identified adverse events that prompted discontinuation; FDA's manual review of the narratives also yielded 8 patients who discontinued due to excessive toxicity and four patients who experienced an AE leading to discontinuation, totaling 12 patients (10%) in among all patients (n=117) in Trial 12-230 who discontinued naxitamab due to treatment-emergent toxicity as detailed in Table 8-30. This is consistent with the Applicant's description above. Six of these patients (8.3%) received the recommended phase 2 dose of naxitamab and were included in FDA's primary safety analysis for Trial 12-230 (n=72).

{DANYELZA, naxitamab-gqgk}

Table 8-30: Discontinuations due to Adverse Events, Trial 12-230*

Disposition Category	Adverse Events for Individual Patients
Discontinued due to excessive toxicity	(b) (6): anaphylaxis (b) (6): anaphylaxis (b) (6): hypotension (b) (6): acute kidney injury (b) (6): angioedema (b) (6): mental status changes, hypotension ** (b) (6): hypertension ** (b) (6): several non-serious adverse events
Adverse event leading to discontinuation	** (b) (6): PRES ** (b) (6): hypertension, pyrexia ** (b) (6): urinary retention, hypertension ** (b) (6): hypertension

*Primary analysis based on review of narratives

**Patient received recommended phase 2 dose of 3.0 mg/kg/dose naxitamab

Patient (b) (6) was a 17-year-old with neuroblastoma in second or greater complete remission who experienced several non-serious adverse events leading to discontinuation after the first three infusions of naxitamab during Cycle 1. The preferred terms associated with the discontinuation included urticaria, hypotension, vomiting, breath sounds abnormal, pain, back pain, headache, nausea, localized edema, platelet count decreased, neck pain, pain in extremity, pyrexia, abdominal pain, non-cardiac chest pain, pruritus, vision blurred, fatigue, erythema multiforme. According to the narrative, he experienced infusion reactions with the terms listed above with each dose and was “taken off study to improve quality of life.”

Narratives for SAEs are summarized in the SAE section above.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant’s Position:

Serious infusion reactions requiring urgent interventions have occurred during naxitamab infusions. These reactions may be mitigated by premedications, supportive medications, infusion interruption, infusion rate reduction, or permanent discontinuation of naxitamab as described in naxitamab product information.

{DANYELZA, naxitamab-gqgk}

The FDA's Assessment:

Action taken with naxitamab in response to specific adverse events was not reliably captured during Trial 12-230 and this information was not included as a standard variable in the adverse event dataset. The Applicant conducted a retrospective review to determine events which impaired compliance (in which the entire calculated weight-based dose was not delivered), resulted in delivery of an incomplete cycle, or had dose interruptions or rate changes recorded. Two patients ((b) (6) and (b) (6)) had a discontinuation or delay due to social reasons (parent withdrew consent after the patient experienced non-serious AEs, and infusion delayed due to the family needing to return home). Nine of 117 patients(8%) had interruptions in naxitamab administration likely attributable to adverse events, though in some cases a corresponding toxicity was not recorded. Table 8-32 lists adverse events leading to treatment interruption. In both trials, the events are almost entirely infusion-related reactions or hypersensitivity events.

Table 8-31: Adverse Events Leading to Treatment Interruption in Trial 12-230

Interruption due to AE which was not recorded	• (b) (6)* • (b) (6)* (respiratory depression and hypotension, inferred from concomitant medication log)
Interruption due to AE	• (b) (6) (Grade 4 wheezing) • (b) (6)* (full-body rash) • (b) (6)* (multiple events during two infusions: hypotension, cough, wheezing, Grade 3 hypoxia) • (b) (6)* (Grade 2 hypotension, Grade 3 acidosis) • (b) (6)* (urticaria, flushing, pain and hypotension) • (b) (6) (urticaria, sinus tachycardia, flushing, fever, dyspnea, chills) • (b) (6) (nausea, pain)

Source: Primary review, CSR Trial 12-230

*Patient received recommended phase 2 dose of 3.0 mg/kg/dose naxitamab

{DANYELZA, naxitamab-gqgk}

Table 8-32: Adverse Events Leading to Treatment Interruption in Trial 201

Preferred Term	All Grades (n)	All Grades (%)	Grades 3 - 4 (n)	Grade 3 - 4 (%)
Hypotension	20	80.0%	14	56.0%
Bronchospasm	4	16.0%	2	8.0%
Abdominal pain	1	4.0%	1	4.0%
Anaphylactic reaction	1	4.0%	1	4.0%
Hypersensitivity	1	4.0%	0	0.0%
Lethargy	1	4.0%	0	0.0%
Urticaria	1	4.0%	0	0.0%

*Source: Primary review, adae.xpt***Significant Adverse Events**The Applicant's Position:

The significant AEs reported are described in other sections of this document.

The FDA's Assessment:

Please see description of serious adverse events and adverse events of special interest.

Treatment-Emergent Adverse Events and Adverse ReactionsThe Applicant's Position:**Treatment-Emergent Adverse Events (TEAEs)**

In Trial 12-230, the percentage of subjects reporting at least one TEAE was 99.1% in SAF and 97.7% in PAS. TEAEs occurring in at least 50% of SAF subjects included pain (98.3%), hypotension (82.9%), abdominal pain (81.2%), urticaria (79.5%), pyrexia (74.4%), vomiting (61.5%), pain in extremity (60.7%), cough (60.7%), pruritus (59.0%), flushing (55.6%), nausea

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

{DANYELZA, naxitamab-gqgk}

(57.3%), and decreased appetite (52.1%), as well as the laboratory-parameter–associated TEAEs of anaemia (71.8%), lymphocyte count decreased (67.5%), platelet count decreased (65.0%), hypoalbuminaemia (58.1%), hyperglycaemia (53.0%), WBC count decreased (53.0%), and neutrophil count decreased (50.4%). For Trial 11-009 and Trial 12-116, the most common TEAEs reported for subjects were overall similar to those reported for Trial 12-230 SAF subjects.

In Trial 201, the percentage of subjects reporting at least one TEAE was 100%. TEAEs occurring in at least 50% of subjects included pain (100%), hypotension (100%), urticaria (80.0%), bronchospasm (76.0%), tachycardia (76.0%), pyrexia (72.0%), cough (60.0%), vomiting (60.0%), diarrhoea (56.0%), and nausea (56.0%).

In 2PR01, the percentage of patients reporting at least one TEAE was 100%. TEAEs occurring in at least 50% of patients included pain (100%), hypotension (86.5%), tachycardia (82.7%), urticaria (69.2%), bronchospasm (57.7%), and vomiting (53.8%).

Adverse Reactions (Treatment-related TEAEs)

Trial 12-230

In 12-230 SAF subjects, 98.3% reported at least one treatment-related TEAE (see Table 8-33). Treatment-related TEAEs reported for at least 50% of subjects included pain (98.3%), hypotension (82.9%), abdominal pain (80.3%), urticaria (77.8%), pyrexia (71.8%), vomiting (58.1%), pruritus (56.4%), pain in extremity (54.7%), nausea (53.0%), and flushing (53.0%). More than three-fourths of the treatment-related TEAEs reported in the SAF were infusion-related (77.9%). Pain accounted for the largest proportion of infusion-related TEAEs (20.2%) and was reported for almost all Trial 12-230 SAF subjects (98.3%). Other commonly reported infusion-related TEAEs for subjects in SAF group included hypotension (81.2%), abdominal pain (76.1%), urticaria (76.1%), pyrexia (59.8%), vomiting (54.7%), and flushing (53.0%).

Pain was also reported by other terms such as noncardiac chest pain, facial pain, chest pain, abdominal pain, abdominal pain upper, oral pain, oropharyngeal pain, pain in extremity, back pain, neck pain, musculoskeletal pain, bone pain, musculoskeletal chest pain, pain in jaw, urinary tract pain, penile pain, vulvovaginal pain, genital pain, scrotal pain, testicular pain, ear pain, and lymph node pain. The pool of these terms account for about 28.5% of all treatment-related TEAEs reported for subjects in the SAF.

When evaluated by a pain score, the highest scores for pain were reported during the 30-minute naxitamab infusion, with pain subsiding before hospital discharge.

The reported treatment-related TEAEs of peripheral sensory neuropathy, paraesthesia, peripheral motor neuropathy, and neuralgia, were all nonserious Grades 1 or 2.

{DANYELZA, naxitamab-gqgk}

Table 8-33 Summary of Treatment-Related Treatment-Emergent Adverse Events Reported for at least 10% of Trial 12-230 Subjects in the Safety Analysis Set

System Organ Class/ Preferred Term	Overall (N=117) [n(%) #events]
Total number of treatment-related TEAEs reported, including those that were reported in less than 5% of subjects	5090
Number of subjects with at least one related TEAE reported	115 (98.3)
General disorders and administration site conditions	115 (98.3), 1408
Pain	115 (98.3), 836
Pyrexia	84 (71.8), 242
Face oedema	40 (34.2), 72
Injection site reaction	40 (34.2), 86
Fatigue	28 (23.9), 34
Localised oedema	26 (22.2), 40
Chills	16 (13.7), 20
Vascular disorders	109 (93.2), 586
Hypotension	97 (82.9), 350
Flushing	62 (53.0), 182
Hypertension	20 (17.1), 40
Gastrointestinal disorders	108 (92.3), 653
Abdominal pain	94 (80.3), 288
Vomiting	68 (58.1), 162
Nausea	62 (53.0), 111
Diarrhoea	38 (32.5), 61
Skin and subcutaneous tissue disorders	107 (91.5), 637
Urticaria	91 (77.8), 320
Pruritus	66 (56.4), 175
Erythema multiforme	26 (22.2), 34
Erythema	21 (17.9), 45
Hyperhidrosis	12 (10.3), 31
Respiratory, thoracic and mediastinal disorders	87 (74.4), 422
Cough	57 (48.7), 121
Wheezing	45 (38.5), 85
Bronchospasm	23 (19.7), 53
Dyspnoea	20 (17.1), 30
Stridor	20 (17.1), 28
Oropharyngeal pain	18 (15.4), 31
Hypoxia	13 (11.1), 18
Musculoskeletal and connective tissue disorders	80 (68.4), 249
Pain in extremity	64 (54.7), 128
Back pain	37 (31.6), 74
Neck pain	22 (18.8), 25
Investigations	69 (59.0), 688
Platelet count decreased	56 (47.9), 465
White blood cell count decreased	39 (33.3), 164

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	Overall (N=117) [n(%) #events]
Breath sounds abnormal	15 (12.8), 25
Metabolism and nutrition disorders	50 (42.7), 82
Decreased appetite	43 (36.8), 64
Nervous system disorders	49 (41.9), 112
Peripheral sensory neuropathy	23 (19.7), 39
Headache	20 (17.1), 26
Lethargy	12 (10.3), 19
Cardiac disorders	42 (35.9), 99
Sinus tachycardia	40 (34.2), 92
Psychiatric disorders	42 (35.9), 81
Anxiety	25 (21.4), 49
Irritability	16 (13.7), 21

Note: Subjects are counted only once in each column for which they have an enrollment and only AEs associated with the enrollment are presented.

TEAE = treatment-emergent adverse events.

Trial 201

All Trial 201 subjects (25 [100%]) experienced at least one TEAE considered to be related to naxitamab treatment (see Table 8-34). The most commonly reported related TEAEs were known reactions to infusion of naxitamab. These included pain (100%), hypotension (100%), urticaria (80.0%), bronchospasm (76.0%), tachycardia (76.0%), and pyrexia (64%); five of these were also reported as treatment-related TEAEs for at least 50% of Trial 12-230 SAF subjects (i.e., pain, hypotension, pyrexia, urticaria, and cough). The reported treatment-related TEAEs of peripheral sensory neuropathy, paraesthesia, and neuralgia, were all nonserious Grades 1 or 2.

Table 8-34 Summary of Treatment-related Treatment-Emergent Adverse Events Experienced by at least 10% of Trial 201 Subjects

System Organ Class/ Preferred Term	Trial 201 Subjects (N=25) [n(%), #events]
Subjects with at least one related TEAE where the drug is Naxitamab	25 (100), 1218
General disorders and administration site conditions	25 (100), 429
Pain	25 (100), 338
Pyrexia	16 (64.0), 61
Oedema	7 (28.0), 9
Asthenia	4 (16.0), 6
Fatigue	4 (16.0), 5
Face oedema	3 (12.0), 3
Respiratory, thoracic and mediastinal disorders	25 (100), 146

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	Trial 201 Subjects (N=25) [n(%), #events]
Bronchospasm	19 (76.0), 90
Cough	13 (52.0), 23
Wheezing	7 (28.0), 11
Stridor	4 (16.0), 5
Dyspnoea	3 (12.0), 3
Rhinorrhoea	3 (12.0), 3
Vascular disorders	25 (100), 171
Hypotension	25 (100), 146
Hypertension	11 (44.0), 24
Gastrointestinal disorders	22 (88.0), 66
Vomiting	12 (48.0), 17
Diarrhoea	9 (36.0), 17
Abdominal pain	8 (32.0), 15
Nausea	8 (32.0), 9
Lip oedema	4 (16.0), 4
Skin and subcutaneous tissue disorders	22 (88.0), 195
Urticaria	20 (80.0), 174
Pruritus	9 (36.0), 17
Cardiac disorders	21 (84.0), 104
Tachycardia	19 (76.0), 73
Sinus tachycardia	7 (28.0), 30
Musculoskeletal and connective tissue disorders	14 (56.0), 33
Pain in extremity	10 (40.0), 23
Bone pain	3 (12.0), 3
Neck pain	3 (12.0), 3
Nervous system disorders	14 (56.0), 30
Headache	7 (28.0), 13
Neuralgia	4 (16.0), 5
Paraesthesia	4 (16.0), 5
Eye disorders	6 (24.0), 10
Mydriasis	4 (16.0), 4
Vision blurred	3 (12.0), 4
Immune system disorders	4 (16.0), 9
Anaphylactic reaction	3 (12.0), 4
Metabolism and nutrition disorders	4 (16.0), 6
Decreased appetite	4 (16.0), 4
Injury, poisoning and procedural complications	3 (12.0), 3
Infusion-related reaction	3 (12.0), 3

For Trial 11-009 and Trial 12-116, the most common treatment-related TEAEs reported for subjects were similar to the most common treatment-related TEAEs reported for Trial 12-230 subjects in the SAF.

{DANYELZA, naxitamab-gqgk}

2PR01

In 2PR01, all patients (52) experienced at least one TEAE considered related to naxitamab. All patients had at least one naxitamab-related event of pain in their medical records. Other commonly collected naxitamab-related TEAEs were hypotension (86.5%), tachycardia (82.7%), urticaria (69.2%), bronchospasm (57.7%), and vomiting (50.0%). Pain, hypotension, urticaria, and vomiting were also reported as treatment-related TEAEs for at least 50% of subjects in Trial 12-230 SAF.

Grade 3 and Higher TEAEs

In Trial 12-230 SAF, the percentage of subjects reporting at least one Grade 3+ TEAE was 78.6%. Grade 3+ TEAEs reported for at least 10% of all subjects in the SAF included stridor (13.7%), hypoxia (11.1%), as well as laboratory-parameter-associated TEAEs of lymphocyte count decreased (40.2%), neutrophil count decreased (27.4%), platelet count decreased (24.8%), anemia (23.1%), WBC decreased (20.5%), , and hypokalaemia (19.7%). For subjects in Trials 11-009 and 12-116, the most common TEAEs reported at Grade 3+ were also reported for a similar percentage as for the subjects in Trial 12-230 SAF.

In Trial 201, the percentage of subjects reporting at least one Grade 3+ TEAE was 92%. Grade 3+ TEAEs reported by at least 10% of subjects included pain (72.0%), hypotension (60.0%), urticaria (40.0%), bronchospasm (28.0%), depressed level of consciousness (16.0%), anaphylactic reaction (12.0%), and abdominal pain (12.0%).

In 2PR01, the percentage of patients reporting at least one Grade 3+ TEAE was 100%. Grade 3+ TEAEs reported by at least 10% of patients included pain (96.2%), hypotension (65.4%), urticaria (48.1%), bronchospasm (21.2%), and rash (21.2%).

Grade 3 and higher Adverse Reactions (Treatment-related TEAEs)

In Trial 12-230 SAF, treatment-related Grade 3+ TEAEs reported for two or more subjects included stridor (13.7%), hypoxia (8.5%), hypotension (5.1%), hypertension (5.1%), urticaria (4.3%), diarrhoea (2.6%), vomiting (1.7%), pyrexia (1.7%), anaphylactic reaction (1.7%), and PRES (1.7%), as well as laboratory-parameter-associated TEAEs of platelet count decreased (16.2%), WBC count decreased (15.4%), alanine aminotransferase increased (3.4%), aspartate aminotransferase increased (2.6%), neutrophil count decreased (1.7%).

In Trial 201, treatment-related Grade 3+ TEAEs reported for two or more subjects included pain (72.0%), hypotension (60.0%), urticaria (40.0%), bronchospasm (28.0%), abdominal pain (12%), anaphylactic reaction (12%), stridor (8%), and headache (8%).

{DANYELZA, naxitamab-gqgk}

In 2PR01, treatment-related TEAEs reported for two or more patients included pain (96.2%), hypotension (65.4%), urticaria (48.1%), bronchospasm (21.2%), rash (21.2%), hypoxia (7.7%), abdominal pain (7.7%), hypertension (5.8%), angioedema (5.8%), anaphylactic reaction (5.8%), and anaphylactic shock (3.8%).

Conclusion/Summary

Common treatment-related events were mainly Grades 1 or 2 and included pain (including pain, abdominal pain, and pain in extremity), pyrexia, urticaria, pruritus, nausea, vomiting, hypotension, hypertension, and bronchospasm. More than 75% of treatment-related events were infusion-related. Generally, the highest scores for pain were reported during the 30-minute naxitamab infusion, with pain subsiding before hospital discharge.

Grade 3+ treatment-related events of importance included anaphylaxis, angioedema, hypotension, bronchospasm, and hypertension. The incidence of treatment-related SAEs across trials was consistent and below 30%. No fatal events were reported.

The FDA's Assessment:

FDA's primary analysis of treatment-emergent adverse events focused on the population of patients who received the recommended phase 2 dose of naxitamab in Trial 12-230 and all patients in Trial 201. In a single arm trial, FDA considers all treatment-emergent adverse events in its analysis and cannot confirm the analysis of treatment relatedness nor the discussion of "adverse reactions" provided by the Applicant above. Tables including all treatment-emergent adverse events were provided by the Applicant below. FDA edited Table 8-35 by removing TEAEs with an incidence of < 10% and laboratory-based TEAEs in the investigations SOC, as these will be evaluated based on the ADLB dataset. In general FDA's analysis of non-laboratory related TEAEs was in agreement with that produced by the sponsor with some minor discrepancies generally consisting of only 1 – 2 patients. FDA added columns which include the calculation based on FDA's assessment, where discrepant.

The tables below provide analyses by preferred term with no pooling of related terms. For an analysis of adverse events with pooled terms, refer to the discussion of submission-specific safety issues in section 8.2.5 and to the final product labeling.

{DANYELZA, naxitamab-gqgk}

Table 8-35: Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term Corresponding Treatment-Related Adverse Events, Grade 3 or Higher, and Treatment-Related Grade 3 or Higher Trial 12-230 Phase 1 and 2 Subjects with Dose of 3mg/kg (Safety Analysis Set) (Applicant's Analysis)

System Organ Class/ Preferred Term	All TEAEs (N=72) [n(%)]	All Related TEAEs (N=72) [n(%)]	All Grade 3+ TEAEs (N=72) [n(%)]	All Related Grade 3+ TEAEs (N=72) [n(%)]	FDA All TEAEs (N=72)	FDA Grade 3+ TEAEs (N=72)
Number of TEAEs	4796	3181	596	231		
Subjects with at least one TEAE	71 (98.6)	69 (95.8)	61 (84.7)	45 (62.5)	72 (100)	64 (88.9)
Metabolism and nutrition disorders	69 (95.8)	38 (52.8)	24 (33.3)	2 (2.8)	-	-
Decreased appetite	38 (52.8)	32 (44.4)	3 (4.2)	0	-	-
General disorders and administration	68 (94.4)	68 (94.4)	4 (5.6)	2 (2.8)	-	-
Pain	68 (94.4)	68 (94.4)	1 (1.4)	0	-	-
Pyrexia	52 (72.2)	51 (70.8)	2 (2.8)	1 (1.4)	-	-
Fatigue	32 (44.4)	19 (26.4)	0	0	-	-
Face oedema	24 (33.3)	19 (26.4)	0	0	-	-
Injection site reaction	20 (27.8)	18 (25.0)	0	0	-	-
Localised oedema	18 (25.0)	13 (18.1)	0	0	-	-
Chills	11 (15.3)	8 (11.1)	0	0	-	-
Vascular disorders	68 (94.4)	68 (94.4)	11 (15.3)	8 (11.1)	-	-
Hypotension	64 (88.9)	64 (88.9)	7 (9.7)	4 (5.6)	-	6 (8.3)
Flushing	37 (51.4)	35 (48.6)	0	0	-	-
Hypertension	20 (27.8)	16 (22.2)	5 (6.9)	5 (6.9)	-	-
Gastrointestinal disorders	67 (93.1)	66 (91.7)	6 (8.3)	4 (5.6)	-	-
Abdominal pain	55 (76.4)	55 (76.4)	0	0	-	-
Vomiting	45 (62.5)	43 (59.7)	2 (2.8)	2 (2.8)	-	-
Nausea	40 (55.6)	39 (54.2)	1 (1.4)	1 (1.4)	-	-
Diarrhoea	36 (50.0)	30 (41.7)	3 (4.2)	2 (2.8)	-	-
Constipation	11 (15.3)	5 (6.9)	0	0	-	-
Investigations	66 (91.7)	60 (83.3)	45 (62.5)	28 (38.9)	-	-
Breath sounds abnormal	11 (15.3)	11 (15.3)	0	0	-	-

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	All TEAEs (N=72) [n(%)]	All Related TEAEs (N=72) [n(%)]	All Grade 3+ TEAEs (N=72) [n(%)]	All Related Grade 3+ TEAEs (N=72) [n(%)]	FDA All TEAEs (N=72)	FDA Grade 3+ TEAEs (N=72)
Skin and subcutaneous tissue disorders	62 (86.1)	62 (86.1)	3 (4.2)	3 (4.2)	-	-
Urticaria	51 (70.8)	49 (68.1)	3 (4.2)	3 (4.2)	50 (69.4)	-
Pruritus	38 (52.8)	37 (51.4)	0	0	-	-
Erythema multiforme	24 (33.3)	23 (31.9)	0	0	-	-
Hyperhidrosis	12 (16.7)	12 (16.7)	0	0	-	-
Erythema	8 (11.1)	8 (11.1)	0	0	-	-
Respiratory, thoracic and mediastinal	57 (79.2)	53 (73.6)	18 (25.0)	15 (20.8)	-	-
Cough	41 (56.9)	33 (45.8)	0	0	-	-
Wheezing	27 (37.5)	27 (37.5)	0	0	-	-
Bronchospasm	16 (22.2)	16 (22.2)	0	0	-	-
Dyspnoea	16 (22.2)	15 (20.8)	1 (1.4)	0	-	-
Stridor	16 (22.2)	15 (20.8)	11 (15.3)	11 (15.3)	15 (20.8)	-
Oropharyngeal pain	11 (15.3)	9 (12.5)	0	0	-	-
Rhinorrhoea	11 (15.3)	1 (1.4)	0	0	-	-
Hypoxia	10 (13.9)	8 (11.1)	7 (9.7)	5 (6.9)	-	6 (8.3)
Musculoskeletal and connective tissue	53 (73.6)	52 (72.2)	0	0	-	-
Pain in extremity	44 (61.1)	43 (59.7)	0	0	-	-
Back pain	25 (34.7)	24 (33.3)	0	0	-	-
Neck pain	16 (22.2)	15 (20.8)	0	0	-	-
Blood and lymphatic system disorders	46 (63.9)	3 (4.2)	21 (29.2)	1 (1.4)	-	-
Anaemia	46 (63.9)	1 (1.4)	21 (29.2)	0	71 (98.6)	30 (41.7)
Nervous system disorders	38 (52.8)	30 (41.7)	6 (8.3)	3 (4.2)	-	-
Peripheral sensory neuropathy	14 (19.4)	14 (19.4)	0	0	-	-
Headache	13 (18.1)	9 (12.5)	0	0	-	-
Lethargy	10 (13.9)	6 (8.3)	0	0	-	-
Psychiatric disorders	36 (50.0)	33 (45.8)	3 (4.2)	0	-	-
Anxiety	19 (26.4)	18 (25.0)	0	0	-	-
Irritability	18 (25.0)	15 (20.8)	0	0	-	-
Cardiac disorders	34 (47.2)	30 (41.7)	2 (2.8)	0	-	-
Sinus tachycardia	32 (44.4)	28 (38.9)	1 (1.4)	0	-	-

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

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	All TEAEs (N=72) [n(%)]	All Related TEAEs (N=72) [n(%)]	All Grade 3+ TEAEs (N=72) [n(%)]	All Related Grade 3+ TEAEs (N=72) [n(%)]	FDA All TEAEs (N=72)	FDA Grade 3+ TEAEs (N=72)
Infections and infestations	29 (40.3)	1 (1.4)	6 (8.3)	0	-	-
Rhinovirus infection	10 (13.9)	0	0	0	-	-
Eye disorders	18 (25.0)	13 (18.1)	0	0	-	-
Vision blurred	8 (11.1)	6 (8.3)	0	0	-	-
Injury, poisoning and procedural	16 (22.2)	9 (12.5)	0	0	-	-
Contusion	11 (15.3)	8 (11.1)	0	0	-	-

Note: Subjects could enroll multiple times and possibly in both phases (i.e., enrollment in Phase 1 and 2 or twice in Phase 2). N represents unique subjects.

Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of unique subjects who experienced at least one AE in that SOC or PT. Subjects who experienced more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.

Note: Enrollment cut off date for subject population is 15Jan2018. Data cutoff is 15May2018 for efficacy and 17Dec2018 for safety.

Table 8-36: Summary of Treatment Emergent Adverse Events Reported by at least 10% of Subjects in Trial 201, Corresponding Treatment-related Adverse Events, Grade 3 or Higher and Treatment-related Grade 3 or Higher Adverse Events (Applicant's Analysis)

System Organ Class/ Preferred Term	All TEAEs (N=25) [n(%)]	Related TEAEs (N=25) [n(%)]	Grade3+ TEAEs (N=25) [n(%)]	Related Grade 3+ TEAEs (N=25) [n(%)]
Subjects with at least one TEAE	25 (100.0)	25 (100.0)	23 (92.0)	22 (88.0)
General disorders and administration site conditions	25 (100.0)	25 (100.0)	18 (72.0)	18 (72.0)
Pain	25 (100.0)	25 (100.0)	18 (72.0)	18 (72.0)
Pyrexia	18 (72.0)	16 (64.0)	0	0
Oedema	7 (28.0)	7 (28.0)	0	0
Fatigue	6 (24.0)	4 (16.0)	0	0
Face oedema	5 (20.0)	3 (12.0)	0	0
Asthenia	4 (16.0)	4 (16.0)	0	0
Respiratory, thoracic and mediastinal disorders	25 (100.0)	25 (100.0)	11 (44.0)	11 (44.0)
Bronchospasm	19 (76.0)	19 (76.0)	7 (28.0)	7 (28.0)
Cough	15 (60.0)	13 (52.0)	0	0
Wheezing	7 (28.0)	7 (28.0)	0	0
Rhinorrhoea	6 (24.0)	3 (12.0)	0	0

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	All TEAEs (N=25) [n(%)]	Related TEAEs (N=25) [n(%)]	Grade3+ TEAEs (N=25) [n(%)]	Related Grade 3+ TEAEs (N=25) [n(%)]
Stridor	4 (16.0)	4 (16.0)	2 (8.0)	2 (8.0)
Dyspnoea	3 (12.0)	3 (12.0)	0	0
Vascular disorders	25 (100.0)	25 (100.0)	15 (60.0)	15 (60.0)
Hypotension	25 (100.0)	25 (100.0)	15 (60.0)	15 (60.0)
Hypertension	11 (44.0)	11 (44.0)	1 (4.0)	1 (4.0)
Gastrointestinal disorders	24 (96.0)	22 (88.0)	5 (20.0)	3 (12.0)
Vomiting	15 (60.0)	12 (48.0)	1 (4.0)	0
Diarrhoea	14 (56.0)	9 (36.0)	2 (8.0)	0
Nausea	14 (56.0)	8 (32.0)	0	0
Abdominal pain	8 (32.0)	8 (32.0)	3 (12.0)	3 (12.0)
Lip oedema	4 (16.0)	4 (16.0)	1 (4.0)	1 (4.0)
Skin and subcutaneous tissue disorders	22 (88.0)	22 (88.0)	10 (40.0)	10 (40.0)
Urticaria	20 (80.0)	20 (80.0)	10 (40.0)	10 (40.0)
Pruritus	10 (40.0)	9 (36.0)	0	0
Cardiac disorders	21 (84.0)	21 (84.0)	1 (4.0)	1 (4.0)
Tachycardia	19 (76.0)	19 (76.0)	1 (4.0)	1 (4.0)
Sinus tachycardia	7 (28.0)	7 (28.0)	0	0
Nervous system disorders	20 (80.0)	14 (56.0)	6 (24.0)	3 (12.0)
Headache	7 (28.0)	7 (28.0)	2 (8.0)	2 (8.0)
Depressed level of consciousness	6 (24.0)	0	4 (16.0)	0
Neuralgia	4 (16.0)	4 (16.0)	0	0
Paraesthesia	4 (16.0)	4 (16.0)	0	0
Musculoskeletal and connective tissue disorders	16 (64.0)	14 (56.0)	2 (8.0)	2 (8.0)
Pain in extremity	12 (48.0)	10 (40.0)	1 (4.0)	1 (4.0)
Bone pain	3 (12.0)	3 (12.0)	1 (4.0)	1 (4.0)
Neck pain	3 (12.0)	3 (12.0)	1 (4.0)	1 (4.0)
Infections and infestations	12 (48.0)	1 (4.0)	1 (4.0)	0
Influenza	3 (12.0)	0	0	0
Rhinovirus infection	3 (12.0)	0	0	0
Upper respiratory tract infection	3 (12.0)	0	0	0
Blood and lymphatic system disorders	8 (32.0)	3 (12.0)	4 (16.0)	1 (4.0)
Anaemia	4 (16.0)	0	1 (4.0)	0
Thrombocytopenia	3 (12.0)	2 (8.0)	1 (4.0)	1 (4.0)
Investigations	8 (32.0)	2 (8.0)	2 (8.0)	0
Weight decreased	3 (12.0)	1 (4.0)	0	0
Renal and urinary disorders	8 (32.0)	2 (8.0)	0	0
Azotaemia	3 (12.0)	0	0	0
Eye disorders	7 (28.0)	6 (24.0)	0	0
Mydriasis	4 (16.0)	4 (16.0)	0	0
Vision blurred	3 (12.0)	3 (12.0)	0	0
Metabolism and nutrition disorders	6 (24.0)	4 (16.0)	0	0
Decreased appetite	4 (16.0)	4 (16.0)	0	0

{DANYELZA, naxitamab-gqgk}

System Organ Class/ Preferred Term	All TEAEs (N=25) [n(%)]	Related TEAEs (N=25) [n(%)]	Grade3+ TEAEs (N=25) [n(%)]	Related Grade 3+ TEAEs (N=25) [n(%)]
Hyponatraemia	3 (12.0)	1 (4.0)	0	0
Immune system disorders	4 (16.0)	4 (16.0)	3 (12.0)	3 (12.0)
Anaphylactic reaction	3 (12.0)	3 (12.0)	3 (12.0)	3 (12.0)
Injury, poisoning and procedural	4 (16.0)	3 (12.0)	0	0
Infusion related reaction	3 (12.0)	3 (12.0)	0	0
Psychiatric disorders	4 (16.0)	2 (8.0)	0	0
Anxiety	3 (12.0)	2 (8.0)	0	0

Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects experienced at least one AE in that SOC or PT. Subjects who experienced more than one AE in a given SOC or PT were counted only once for that particular SOC or PT. Data cut-off is 12 Jun 2019.

Table 8-37, which includes Grade 3 and greater treatment emergent AEs regardless of the assessment of relatedness, was provided by the Applicant. In general, FDA agrees with the Applicant's analysis below, though some of the numbers in the table below differed slightly from FDA's analysis. Grade 3 or greater device-related infection occurred in 5.1% of patients in Trial 12-230. FDA generally relies on laboratory data reported in the laboratory dataset rather than those reported as AEs. Discrepancies in the FDA analysis for non-laboratory based AEs included hypoxia (10%), hypotension (7%), and pain (0%).

Table 8-37 Summary of Treatment Emergent Adverse Events Grade 3 and Higher Reported in at least 10% of Subjects by Study (Safety Analysis Set) (Applicant's Analysis)

		12-230 Grade 3+		201 Grade 3+	
		(N=117)		(N=25)	
System Organ Class	Preferred Term	All TEAE	Related TEAE	All TEAE	Related TEAE
Investigations	Lymphocyte count	47 (40.2%)	0	1 (4.0%)	1 (4.0%)
	Neutrophil count	32 (27.4%)	2 (1.7%)	0	0
	Platelet count decreased	29 (24.8%)	19 (16.2%)	1 (4.0%)	0

{DANYELZA, naxitamab-gqgk}

		12-230 Grade 3+		201 Grade 3+	
		(N=117)		(N=25)	
System Organ Class	Preferred Term	All TEAE	Related TEAE	All TEAE	Related TEAE
	White blood cell count decreased	24 (20.5%)	18 (15.4%)	0	0
Blood and lymphatic system disorders	Anaemia	27 (23.1%)	0	1 (4.0%)	0
Metabolism and nutrition disorders	Hypokalaemia	23 (19.7%)	1 (0.9%)	0	0
Respiratory, thoracic and mediastinal disorders	Stridor	16 (13.7%)	16 (13.7%)	2 (8.0%)	2 (8.0%)
	Hypoxia	13 (11.1%)	10 (8.5%)	2 (8.0%)	1 (4.0%)
	Bronchospasm	0	0	7 (28.0%)	7 (28.0%)
Vascular disorders	Hypotension	10 (8.5%)	6 (5.1%)	15 (60.0%)	15 (60.0%)
Skin and subcutaneous tissue disorders	Urticaria	5 (4.3%)	5 (4.3%)	10 (40.0%)	10 (40.0%)
Immune system disorders	Anaphylactic reaction	2 (1.7%)	2 (1.7%)	3 (12.0%)	3 (12.0%)
General disorders and administration site conditions	Pain	1 (0.9%)	0	18 (72.0%)	18 (72.0%)
Nervous system disorders	Depressed level of consciousness	0	0	4 (16.0%)	0
Gastrointestinal disorders	Abdominal pain	0	0	3 (12.0%)	3 (12.0%)

Note: For Trial 12-230, laboratory TEAEs: Due to the data capture process at MSK not treatment-related TEAEs represent both not treatment-related TEAEs and data entries which do not live up to the definition of a TEAE. Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects experienced at least one grade 3 or higher AE in that SOC or PT. Subjects who experienced more than one AE in a given SOC or PT were counted only once for that particular SOC or PT. Enrollment cut-off date for 12-230 subject population is 15Jan2018. Data cut-off is 17Dec2018 for safety. Data cut-off for study 201 is 12 Jun 2019.

Table 8-38 contains an analysis of Grade 3 and greater TEAEs performed by the Applicant. FDA confirmed the analysis though numbers differed slightly from the Applicant's; a column was added to reflect the FDA analysis where discrepant. Most of the Grade 3 and greater events included laboratory-based AEs which will be evaluated based on laboratory testing later in this review; the only non-laboratory based AE included below was stridor.

{DANYELZA, naxitamab-gqgk}

Table 8-38: Corresponding Treatment-Related Grade 3 or Higher Trial 12-230 Phase 1 and 2 Subjects with Dose of 3mg/kg (Safety Analysis Set) (Applicant's Analysis)

System Organ Class/ Preferred Term	All Grade 3+ TEAEs (N=72) [n(%)]	All Related Grade 3+ TEAEs (N=72) [n(%)]	FDA Analysis All Grade 3+ TEAEs (N=72)
Subjects with at least one grade 3 or higher TEAE	61 (84.7)	45 (62.5)	64 (88.9)
Investigations	45 (62.5)	28 (38.9)	-
Lymphocyte count decreased	32 (44.4)	0	34 (47.2)
Neutrophil count decreased	27 (37.5)	0	27 (38.9)
Platelet count decreased	22 (30.6)	19 (26.4)	23 (31.9)
White blood cell count decreased	21 (29.2)	17 (23.6)	-
Metabolism and nutrition disorders	24 (33.3)	2 (2.8)	-
Hypokalemia	19 (26.4)	1 (1.4)	-
Blood and lymphatic system	21 (29.2)	1 (1.4)	-
Anemia	21 (29.2)	0	30 (41.7)
Respiratory, thoracic and	18 (25.0)	15 (20.8)	-
Stridor	11 (15.3)	11 (15.3)	-

Note: Subjects could enroll multiple times and possibly in both phases (i.e., enrollment in Phase 1 and 2 or twice in Phase 2). N represents unique subjects.

Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of unique subjects who experienced at least one AE in that SOC or PT. Subjects who experienced more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.

Note: Enrollment cut off date for subject population is 15Jan2018. Data cutoff is 15May2018 for efficacy and 17Dec2018 for safety.

Date: 10JUL2020

Data Source: ADAE.sas7bdat, ADSL.sas7bdat

Program Source: TRFI23_2b.sas

Laboratory Findings

The Applicant's Position:

Clinical Chemistry

Renal function

Overall, increased levels of serum creatine were infrequently seen. Only four SAEs on renal function were reported (three acute kidney injury and one renal failure). Two SAEs were not related to naxitamab treatment, and in the other two, confounding factors were present: in one, preceding severe nausea and vomiting occurred, and in the other, 3 drugs were co-suspected (naxitamab, GM-CSF, and antibiotics).

Liver function

Abnormal laboratory values associated with liver function were expected in subject populations for the naxitamab trials, given the nature of their disease, prior exposure to anticancer therapy, and wide inclusion/exclusion criteria.

No significant trends were observed across cycles for clinical chemistry parameters associated with liver function tests and there was no indication of drug-induced liver injury (DILI).

Hematology

Abnormal hematology values were expected in subject populations for the naxitamab trials, given the nature of their disease, prior exposure to anticancer therapy, wide inclusion/exclusion criteria, allowed transfusions, and bone marrow stimulations prior to inclusion.

There was no sign of myelotoxicities despite the high number of hematological laboratory TEAEs reported in Trial 12-230. The only observations that seemed to be linked to treatment were the leukocytes and neutrophil counts fluctuating to various degrees during cycles due to GM-CSF treatment. Of SAEs reported across all trials, one febrile neutropenia was related, one SAE neutrophil count decreased related to GM-CSF, two platelet count decreased SAEs were not related, and three SAEs of lymphocyte count decreased were not related.

{DANYELZA, naxitamab-gqgk}

The FDA's Assessment:

The following tables were provided by the Applicant upon request and confirmed by FDA. Minor formatting changes were made to the tables submitted by the Applicant. FDA agrees with the presentation of laboratory abnormalities in Table 8-33 with some minor discrepancies (variation by one patient) in incidences of hypokalemia, decreased lymphocytes, AST increased, and ALT increased. The results of FDA's analysis are shown in **Table 8-40**.

Table 8-39 : Summary of Treatment Emergent Abnormal Laboratory Values by Highest CTCAE Grade Worsening from Baseline in Trial 201 (Applicant's Analysis)

CTCAE Term	N (N=25)	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine aminotransferase increased	24	10 (41.7)	5 (20.8)	3 (12.5)	2 (8.3)	0	2 (8.3)
Hypoalbuminemia	24	12 (50.0)	11 (45.8)	1 (4.2)	0	0	0
Alkaline phosphatase increased	24	2 (8.3)	2 (8.3)	0	0	0	0
Aspartate aminotransferase increased	24	4 (16.7)	4 (16.7)	0	0	0	0
Blood bilirubin increased	24	3 (12.5)	2 (8.3)	0	1 (4.2)	0	1 (4.2)
Creatinine increased	24	1 (4.2)	1 (4.2)	0	0	0	0
Anemia	23	11 (47.8)	2 (8.7)	8 (34.8)	1 (4.3)	0	1 (4.3)
Lymphocyte count decreased	23	15 (65.2)	0	8 (34.8)	5 (21.7)	2 (8.7)	7 (30.4)
Lymphocyte count increased	23	3 (13.0)	0	2 (8.7)	1 (4.3)	0	1 (4.3)
Neutrophil count decreased	23	14 (60.9)	0	5 (21.7)	8 (34.8)	1 (4.3)	9 (39.1)
Platelet count decreased	23	15 (65.2)	9 (39.1)	2 (8.7)	4 (17.4)	0	4 (17.4)
Hypokalemia	24	15 (62.5)	13 (54.2)	0	2 (8.3)	0	2 (8.3)
Hyponatremia	24	7 (29.2)	7 (29.2)	0	0	0	0
White blood cell decreased	23	19 (82.6)	6 (26.1)	10 (43.5)	3 (13.0)	0	3 (13.0)

The table presents laboratory parameters with available grading according to CTCAE version 4.0. For each laboratory parameter N reflects the number of patients with a baseline assessment and at least one post-baseline assessment. The data represent the worst post-baseline worsening of treatment emergent laboratory evaluation

{DANYELZA, naxitamab-gqgk}

compared to baseline. Baseline evaluation was the last non-missing value prior to first naxitamab dosing. The following CTCAE terms, did not have any post-baseline values qualifying for inclusion in the table: Hemoglobin increased, Hyperkalemia, Hyponatremia, Leukocytosis.

Table 8-40: Laboratory Abnormalities (>20%) That Worsened from Baseline in Trial 201 (FDA Analysis)

CTCAE Term	N=25	All Grade n%	Grade 1 n%	Grade 2 n%	Grade 3 n%	Grade 4 n%	Grade 3- 4 n%
Alanine aminotransferase increased	24	10 (41.7)	5 (20.8)	3 (12.5)	2 (8.3)	0	2 (8.3)
Hypoalbuminemia	24	12 (50.0)	11 (45.8)	1 (4.2)	0	0	0
Hypokalemia	24	15 (62.5)	13 (54.2)	0	2 (8.3)	0	2 (8.3)
Hyponatremia	24	7 (29.2)	7 (29.2)	0	0	0	0
Anemia	23	11 (47.8)	2 (8.7)	8 (34.8)	1 (4.3)	0	1 (4.3)
Lymphocyte count decreased	23	17 (73.9)	2 (8.7)	8 (34.8)	5 (21.7)	2 (8.7)	7 (30.4)
Neutrophil count decreased	23	14 (60.9)	0	5 (21.7)	8 (34.8)	1 (4.3)	9 (39.1)
Platelet count decreased	23	15 (65.2)	9 (39.1)	2 (8.7)	4 (17.4)	0	4 (17.4)
White blood cell decreased	23	19 (82.6)	6 (26.1)	10 (43.5)	3 (13.0)	0	3 (13.0)

Source: adae.xpt

Table 8-41: Laboratory Abnormalities in Patients who Received the RP2D of Naxitamab in Trial 12-230, Worsening from Baseline Analysis (FDA Analysis)

CTCAE Term	N=72	All Grade n%	Grade 1 n%	Grade 2 n%	Grade 3 n%	Grade 4 n%	Grade 3- 4 n%
Alanine aminotransferase increased	66	36 (54.5)	18 (27.3)	12 (18.2)	6 (9.1)	0	6 (9.1)
Hypoalbuminaemia	71	48 (67.6)	35 (49.3)	8 (11.3)	5 (7.0)	0	5 (7.0)
Aspartate aminotransferase increased	70	34 (48.6)	27 (38.6)	4 (5.7)	3 (4.3)	0	3 (4.3)
Hypocalcaemia	72	46 (63.9)	18 (25.0)	22 (30.6)	3 (4.2)	3 (4.2)	6 (8.3)
Hyperglycaemia	72	53 (73.6)	35 (48.6)	18 (25.0)	0	0	0
Hypoglycaemia	72	21 (29.2)	5 (6.9)	10 (13.9)	5 (6.9)	1 (1.4)	6 (8.3)
Hypomagnesaemia	61	33 (54.1)	31 (50.8)	2 (3.3)	0	0	0
Hypophosphataemia	19	9 (47.4)	2 (10.5)	6 (31.6)	1 (5.3)	0	1 (5.3)
Hypokalaemia	72	34 (47.2)	11 (15.3)	0	18 (25.0)	5 (6.9)	23 (31.9)
Hyponatraemia	72	27 (37.5)	23 (31.9)	0	3 (4.2)	1 (1.4)	4 (5.6)
Anaemia	72	55 (76.4)	6 (8.3)	19 (26.4)	30 (41.7)	0	30 (41.7)
White blood cell decreased	72	50 (69.4)	9 (12.5)	13 (18.1)	16 (22.2)	12 (16.7)	28 (38.9)
Lymphocyte count decreased	72	57 (79.2)	9 (12.5)	8 (11.1)	21 (29.2)	19 (26.4)	40 (55.6)
Neutrophil count decreased	72	52 (72.2)	8 (11.1)	11 (15.3)	14 (19.4)	19 (26.4)	33 (45.8)
Platelet count decreased	72	51 (70.8)	13 (18.1)	9 (12.5)	8 (11.1)	21 (29.2)	29 (40.3)

Source: Primary review, adae.xpt

FDA does not agree that significant myelosuppression was not observed in the trial. As demonstrated in the tables above, severe (Grade 3 – 4) thrombocytopenia (40% of patients in Trial 12-230 and 17 % of patients in Trial 201) and neutropenia (46% of patients in Trial 12-230 and 39% of patients in Trial 201) were not uncommon. FDA agrees that the population of patients enrolled in these trials has been heavily pre-treated, but notes that the tables above include patients with worsening laboratory parameters from baseline.

Based on an analysis performed by the Applicant in Trial 12-230, events of Grade 4 thrombocytopenia lasted 0 – 30 days (median 2 days) and events of Grade 4 neutropenia lasted 0 – 10 days (median 2 days).

{DANYELZA, naxitamab-gqgk}

Some electrolyte perturbations were also observed, with 32% of patients in Trial 12-230 and 8% of patients in Trial 201 experiencing Grade 3 – 4 hypokalemia. Calcium, magnesium and phosphorous were not routinely assessed in Trial 201 and are not included in the table nor in the dataset.

Vital Signs

The Applicant's Position:

Overall, variations in both diastolic blood pressure and systolic blood pressure around naxitamab dosing days were seen, which was anticipated, considering that hypotension is a known infusion-related reaction.

The FDA's Assessment:

Given the differences in age-based norms for individual patients, individual adverse event data for blood pressure (hypotension, hypertension, etc.) provide greater clinical relevance than average data across patients. See discussion of hypertension and hypotension in Section 8.2.5.

Two patients in Trial 12-230 and no patients in Trial 201 experienced events of sinus bradycardia that were reported as AEs; events in both patients occurred on the day of infusion and were assessed as definitely related to naxitamab. Forty-six patients (39.3%) experienced sinus tachycardia (1.7% Grade 3) in Trial 12-230. The majority of events occurred on the day of infusion and were assessed as related to naxitamab. Twenty-one (84%) patients experienced events of tachycardia or sinus tachycardia in Trial 201, with one patient (4%) experiencing a Grade 3 event. Almost all events occurred on the day of a naxitamab infusion.

Reviewer note: Given the prevalence of pain during infusion of naxitamab, the occurrence of tachycardia may be due to pain. Tachycardia may also represent physiologic response to hypotension, which was also experienced during infusions, or as part of hypersensitivity reaction such as anaphylaxis.

Electrocardiograms (ECGs)

The Applicant's Position:

Abnormal ECG findings were observed in Trial 12-230 and Trial 201. In Trial 201, the clinical significance of ECG findings was recorded. None of the observed abnormalities were considered clinically significant by Investigator.

{DANYELZA, naxitamab-gqgk}

One patient in Trial 201 had an unspecified arrhythmia (Grade 2) other than tachycardia recorded as an adverse event, assessed as related and reported as resolved. FDA requested further information regarding this case, described as occasional bradycardia (heart rate as low as 32 – 38 beats per minute) with fast and spontaneous recovery to > 120 beats per minute). This event appears to be isolated and self-resolving.

The FDA's Assessment:

In Trial 12-230, ECGs were planned to be conducted only during Phase 1; the dataset provided a narrative description or result for abnormal ECGs. Fifty-six abnormal ECGs were identified, primarily describing sinus tachycardia. Patients who experienced prolonged QT or borderline prolonged QT are described below; confounding medications are noted where applicable.

Table 8-42: Patients with QT Prolongation in Trial 12-230

Prolonged QT	• (b) (6): Patient had QTc recorded as 509 ms five days after naxitamab infusion. • (b) (6): prolonged QT (QTc 525 ms); no concomitant medications on the day of ECG finding. • (b) (6): Prolonged QT. Multiple confounding concomitant medications (hydroxyzine, famotidine, ondansetron).
Borderline prolonged QT prior to initiation of naxitamab	• (b) (6) • (b) (6)

{DANYELZA, naxitamab-gqgk}

Borderline prolonged QT during treatment	For all patients, concomitant medications included ondansetron, famotidine and hydroxyzine • (b) (6) • (b) (6) • (b) (6)
--	---

CTCAE v 4.03 defines Grade 3 electrocardiogram QT corrected interval prolonged as QTc of 501ms or greater on two separate ECGs. Although two patients had measurements of 501 ms or greater, it is not clear that these were confirmed with repeat measurement.

There were no reported adverse events of QT prolongation. In Trial 201, the datasets indicated that three patients had abnormal ECGs that were not clinically significant. Details regarding these abnormalities were requested by FDA and findings did not include any arrhythmias or QT prolongation. Datasets did not include details such as QT interval as actual ECG measurements were not captured on trial according to the protocol. FDA considered that, due to the low likelihood of direct ion channel interaction, the likelihood of a monoclonal antibody causing QT prolongation is low.

QT

The Applicant's Position:

No QT trials were conducted.

The FDA's Assessment:

FDA has no additional comments. See description of ECG findings above.

Immunogenicity

The Applicant's Position:

The incidence of subjects positive for ADA at one or more samples varied from 8.3% in Trial 201 (using a fully validated assay) to 22.1% in 12-230 and 15.4% in PR01. The median time from first

{DANYELZA, naxitamab-gqgk}

infusion to first positive ADA titer was similar in Trials 201 and 12-230 (20.5 and 19.0 days, respectively), ranging from 12 to 64 days.

The FDA's Assessment:

Please see clinical pharmacology assessment of the impact of ADA in Section 6.3.2 and Section 19.4. The assessment is limited by the lack of a fully validated assay in Trial 12-230 and only two patients with positive ADA post-baseline in Trial 201.

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

The Applicant's Position:

See Section 8.1.2, Trial results.

The FDA's Assessment:

Assessments of pain, which occurred in nearly all patients who received naxitamab in the safety population considered for the BLA, were performed in accordance with standard medical practice and did not include any additional patient-reported outcome assessments. Analyses of events of pain are described in Sections 8.2.4 and 8.2.5.

8.2.6. Safety Analyses by Demographic Subgroups

The Applicant's Position:

In the population PK model, naxitamab exposure was predicted to increase with body weight. In the safety data available, there were no signs of increasing toxicity with increasing body weight.

Age was not a statistically significant covariate in the population PK model. In the age Group 2 to less than 6 years; infusion-related TEAEs of pyrexia, hypotension, bronchospasm, and stridor appeared more frequent. In the age Group 2 to less than 12 years, cough and wheezing appeared more frequently; however, children are known to differ in disease presentation by age.

Safety data do not indicate differences in safety between gender or race.

{DANYELZA, naxitamab-gqgk}

For subjects with prior anti-GD2 therapy, there were no differences in TEAEs reported or serious infusion-related reactions between subjects with or without prior anti-GD2 therapy.

For ADA-positive subjects (Trial 12-230), the relative distribution and frequency of treatment-related TEAEs (including infusion-related TEAEs and Grade 3+ TEAEs) appeared similar between ADA-positive and ADA-negative subjects.

The FDA's Assessment:

The Applicant provided the following tables describing the safety experience by demographic subgroups. FDA confirmed these tables, though numbers differed slightly in the analysis of Trial 12-230. In both trials, it appeared males were more likely to have a Grade 3 or higher TEAE but experienced fewer TEAEs leading to discontinuation. However, given the extremely limited number of patients in the safety population, the differences may be due to chance and extreme caution should be used in interpreting any differences between groups. There did not appear to be significant differences in adverse event trends by age or by race and all analyses are limited by the small number of patients in each of the subgroups.

Table 8-43: Summary of Subjects by Adverse Event Category by Sex (Trial 12-230 Safety Analysis Set) (Applicant's Analysis)

	Male (N=45)	Female (N=27)	All (N=72)
Subjects with at least one TEAE	45 (100.0%)	27 (100.0%)	72 (100.0%)
Subjects with at least one related TEAE	43 (95.6%)	26 (96.3%)	69 (95.8%)
Subjects with at least one TEAE of Grade 3 or higher	42 (93.3%)	22 (81.5%)	64 (88.9%)
Subjects with at least one related TEAE of Grade 3 or higher	30 (66.7%)	15 (55.6%)	45 (62.5%)
Subjects with at least one SAE	21 (46.7%)	8 (29.6%)	29 (40.3%)
Subjects with at least one related SAE	13 (28.9%)	7 (25.9%)	20 (27.8%)
Subjects with at least one TEAE Leading to Death	0	0	0
Subjects who discontinued due to an adverse event or excessive toxicity[1]	3 (6.7%)	3 (11.1%)	6 (8.3%)

[1] Specific adverse events leading to discontinuation were not captured in the EDC system. A combination of investigator and sponsor assessed reason for discontinuing trial was used to get these numbers.

{DANYELZA, naxitamab-gqgk}

FDA agrees with the analysis in Table 8-44.

Table 8-44: Summary of Subjects by Adverse Event Category by Sex (Trial 201 Safety Analysis Set) (Applicant's Analysis)

	Male (N=16)	Female (N=9)	All (N=25)
Subjects with at least one TEAE	16 (100.0%)	9 (100.0%)	25 (100.0%)
Subjects with at least one naxitamab related TEAE	16 (100.0%)	9 (100.0%)	25 (100.0%)
Subjects with at least one TEAE of grade 3 or higher	15 (93.8%)	8 (88.9%)	23 (92.0%)
Subjects with at least one naxitamab related TEAE of grade 3 or higher	15 (93.8%)	7 (77.8%)	22 (88.0%)
Subjects with at least one SAE	4 (25.0%)	4 (44.4%)	8 (32.0%)
Subjects with at least one naxitamab related SAE	2 (12.5%)	3 (33.3%)	5 (20.0%)
Subjects with at least one TEAE leading to death	0	0	0
Subjects with at least one TEAE leading to discontinuation from study	1 (6.3%)	2 (22.2%)	3 (12.0%)

FDA agrees with the analyses in Table 8-44.

{DANYELZA, naxitamab-gqgk}

Table 8-45: Summary of Subjects by Adverse Event Category by Age Group (Trial 12-230 Safety Analysis Set) (Applicant's Analysis)

	<12 (N=65)	12 - <18 years old (N=5)	18 years or older (N=2)	All (N=72)
Subjects with at least one TEAE	65 (100.0%)	5 (100.0%)	2 (100.0%)	72 (100.0%)
Subjects with at least one related TEAE	62 (95.4%)	5 (100.0%)	2 (100.0%)	69 (95.8%)
Subjects with at least one TEAE of Grade 3 or higher	58 (89.2%)	4 (80.0%)	2 (100.0%)	64 (88.9%)
Subjects with at least one related TEAE of Grade 3 or higher	40 (61.5%)	3 (60.0%)	2 (100.0%)	45 (62.5%)
Subjects with at least one SAE	25 (38.5%)	2 (40.0%)	2 (100.0%)	29 (40.3%)
Subjects with at least one related SAE	17 (26.2%)	2 (40.0%)	1 (50.0%)	20 (27.8%)
Subjects with at least one TEAE Leading to Death	0	0	0	0
Subjects who discontinued from the study due to an Adverse Event or Excessive Toxicity[1]	4 (6.2%)	2 (40.0%)	0	6 (8.3%)

[1] Specific adverse events leading to discontinuation were not captured in the EDC system. A combination of investigator and sponsor assessed reason for discontinuing trial was used to get these numbers.

FDA agrees with the analysis in Table 8-45.

Trial 12-230 included 8 patients who were two years old at first enrollment. All (100%) of these patients had a TEAE, and 100% had a TEAE Grade 3 or higher and 50% had an SAE. In Trial 210, there was only one patient less than or equal to two years of age. This patient experienced TEAEs including Grade 3 TEAEs, but no SAEs.

Table 8-46: Summary of Subjects by Adverse Event Category by Age Group (Trial 201 Safety Analysis Set) (Applicant's Analysis)

	<12 (N=25)	12 - <18 years old (N=0)	18 years or older (N=0)	All (N=25)
Subjects with at least one TEAE	25 (100.0%)	0	0	25 (100.0%)

{DANYELZA, naxitamab-gqgk}

	<12 (N=25)	12 - <18 years old (N=0)	18 years or older (N=0)	All (N=25)
Subjects with at least one naxitamab related TEAE	25 (100.0%)	0	0	25 (100.0%)
Subjects with at least one TEAE of grade 3 or higher	23 (92.0%)	0	0	23 (92.0%)
Subjects with at least one naxitamab related TEAE of grade 3 or higher	22 (88.0%)	0	0	22 (88.0%)
Subjects with at least one SAE	8 (32.0%)	0	0	8 (32.0%)
Subjects with at least one naxitamab related SAE	5 (20.0%)	0	0	5 (20.0%)
Subjects with at least one TEAE leading to death	0	0	0	0
Subjects with at least one TEAE leading to discontinuation from study	3 (12.0%)	0	0	3 (12.0%)

FDA agrees with the results in Table 8-46.

Table 8-47 : Summary of Subjects by Adverse Event Category by Race (Trial 12-230 Safety Analysis Set) (Applicant's Analysis)

	Asian / Far East / Indian Subcontinent (N=5)	Black/African American (N=3)	Native American/ American Indian/ Alaska Native/N/C/ (N=2)	White (N=55)	Pt refused to answer (N=5)	Other (N=2)	All (N=72)
Subjects with at least one TEAE	5 (100.0%)	3 (100.0%)	2 (100.0%)	55 (100.0%)	5 (100.0%)	2 (100.0%)	72 (100.0%)
Subjects with at least one related TEAE	5 (100.0%)	3 (100.0%)	1 (50.0%)	53 (96.4%)	5 (100.0%)	2 (100.0%)	69 (95.8%)
Subjects with at least one TEAE of Grade 3 or higher	4 (80.0%)	3 (100.0%)	2 (100.0%)	49 (89.1%)	4 (80.0%)	2 (100.0%)	64 (88.9%)
Subjects with at least one related TEAE of Grade 3 or higher	4 (80.0%)	3(100.0%)	1 (50.0%)	34 (61.8%)	3 (60.0%)	0	45 (62.5%)

{DANYELZA, naxitamab-gqgk}

	Asian / Far East / Indian Subcontinent (N=5)	Black/African American (N=3)	Native American/ American Indian/ Alaska Native/N/C/ (N=2)	White (N=55)	Pt refused to answer (N=5)	Other (N=2)	All (N=72)
Subjects with at least one SAE	3 (60.0%)	2 (66.7%)	0	23 (41.8%)	1 (20.0%)	0	29 (40.3%)
Subjects with at least one related SAE	2 (40.0%)	2 (66.7%)	0	15 (27.3%)	1 (20.0%)	0	20 (27.8%)
Subjects with at least one TEAE leading to death	0	0	0	0	0	0	0
Subjects who discontinued due to an Adverse Event or Excessive Toxicity[1]	1 (20.0%)	1 (33.3%)	0	4 (7.3%)	0	0	6 (8.3%)

[1] Specific adverse events leading to discontinuation were not captured in the EDC system. A combination of investigator and sponsor assessed reason for discontinuing trial was used to get these numbers.

FDA's analysis of the results shown in Table 8-47 demonstrated 100% of the Native American/Native Canadian/Alaska Native group experienced a TEAE and 100% of these patients experienced a Grade 3 or higher TEAE.

Table 8-48: Summary of Subjects by Adverse Event Category by Race (Trial 201 Safety Analysis Set) (Applicant's Analysis)

	Asian (N=12)	Black or African American (N=1)	White (N=12)	All (N=25)
Subjects with at least one TEAE	12 (100.0%)	1 (100.0%)	12 (100.0%)	25 (100.0%)
Subjects with at least one naxitamab related TEAE	12 (100.0%)	1 (100.0%)	12 (100.0%)	25 (100.0%)
Subjects with at least one TEAE of grade 3 or higher	12 (100.0%)	1 (100.0%)	10 (83.3%)	23 (92.0%)
Subjects with at least one naxitamab related TEAE of grade 3 or higher	12 (100.0%)	1 (100.0%)	9 (75.0%)	22 (88.0%)

{DANYELZA, naxitamab-gqgk}

	Asian (N=12)	Black or African American (N=1)	White (N=12)	All (N=25)
Subjects with at least one SAE	3 (25.0%)	1 (100.0%)	4 (33.3%)	8 (32.0%)
Subjects with at least one naxitamab related SAE	2 (16.7%)	0	3 (25.0%)	5 (20.0%)
Subjects with at least one TEAE leading to death	0	0	0	0
Subjects with at least one TEAE leading to discontinuation from study	2 (16.7%)	0	1 (8.3%)	3 (12.0%)

FDA agrees with the results shown in Table 8-48.

8.2.7. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

AESIs included hypotension and bronchospasm occurring on the same day as a naxitamab infusion and hypertension, and PRES starting at any time.

Bronchospasm

In Trial 12-230, treatment-related bronchospasm was reported for 19.7% of SAF subjects. All TEAEs of bronchospasm reported for SAF subjects occurred on the same day as a naxitamab infusion. No Grade 3+ TEAEs of bronchospasm were reported for Trial 12-230 subjects, and no TEAEs of bronchospasm were determined to be serious. In Trials 11-009 and 12-116, treatment-related TEAEs of bronchospasm at any grade were reported for a smaller percentage of subjects than for Trial 12-230 SAF subjects. Grade 3+ TEAEs of bronchospasm and serious events of bronchospasm were not reported for any subjects in Trial 11-009 or Trial 12-116.

In Trial 201, treatment-related TEAEs of bronchospasm was reported for 76.0% of subjects. Treatment-related bronchospasm was reported at Grade 3+ severity for 28.0% of subjects in Trial 201. No TEAEs of bronchospasm reported for Trial 201 subjects were considered serious.

In 2PR01, treatment-related TEAEs of bronchospasm were captured for 57.7% of 2PR01 patients. Grade 3+ treatment-related TEAEs of bronchospasm were captured for 21.2% of

{DANYELZA, naxitamab-gqgk}

2PR01 patients. Two treatment-related TEAEs of bronchospasm reported (3.8% of patients) were considered serious.

Hypotension

In Trial 12-230, treatment-related hypotension was reported for 82.9% of SAF subjects. Infusion-related hypotension was reported for 81.2% of subjects in the SAF. Although TEAEs of hypotension at any grade were frequently reported in Trial 12-230, Grade 3+ and serious events of hypotension were infrequently reported. In Trials 11-009 and 12-116, Grade 3+ TEAEs of hypotension and serious events of hypotension were reported for similar percentages of subjects in Trials 11-009 and 12-116 compared with Trial 12-230 SAF subjects.

In Trial 201, TEAEs of hypotension were reported for all subjects, and all TEAEs of hypotension were naxitamab related. Grade 3+ treatment-related TEAEs of hypotension were reported for 60.0% of subjects. No SAEs of hypotension were reported for Trial 201 subjects.

In 2PR01, TEAEs of hypotension were reported for 86.5% of patients, and all but one TEAE of hypotension were naxitamab-related. Grade 3+ TEAEs of hypotension were collected for 65.4% of 2PR01 patients. All of the Grade 3+ TEAEs of hypotension were naxitamab-related. No TEAEs of hypotension reported for 2PR01 patients were considered serious.

Hypertension

In Trial 12-230, hypertension was reported for 19.7% of SAF subjects. Treatment-related hypertension was reported for 17.1% of SAF subjects. For treatment-related hypertension occurring at the day of naxitamab infusion, 12.0% of SAF subjects reported infusion-related hypertension. Grade 3+ TEAEs of hypertension were infrequent in Trial 12-230, where Grade 3+ TEAEs were reported for 5.1% of SAF subjects and infusion-related TEAEs were reported for 2.6% of SAF subjects. About 30% of TEAEs of hypertension were considered serious. About half of the serious hypertension events started on the day of or 1 calendar day after Cycle 1, Infusion 3, and other serious hypertension started at earlier infusions in Cycle 1. In Trial 11-009 subjects, hypertension was reported for a similar or a slightly smaller percentage than for all subjects in Trial 12-230 SAF. In Trial 12-116, no TEAEs of hypertension were reported.

In Trial 201, treatment-related TEAEs of hypertension were reported for 44.4% of subjects. Only one Grade 3+ treatment-related TEAE of hypertension was reported for one subject (4.0%) in Trial 201. No TEAEs of hypertension reported for Trial 201 subjects were considered serious.

In 2PR01, treatment-related TEAEs of hypertension were captured for 28.8% of patients. Grade 3+ treatment-related TEAEs of hypertension were captured for 5.8% of 2PR01 patients.

{DANYELZA, naxitamab-gqgk}

No TEAEs of hypertension reported for 2PR01 patients were considered serious.

Posterior Reversible Encephalopathy Syndrome

In Trial 12-230, PRES was reported for two Phase 2 subjects. Both TEAEs of PRES were Grade 3 in severity, serious, and related to naxitamab. Neither of the PRES TEAEs was infusion-related, with both events starting 2 to 7 days after Cycle 1, Infusion 3. One subject was discontinued from trial because of PRES, and the other subject continued in the trial. PRES was not reported for Trial 201 subjects, Trial 11-009 subjects, Trial 12-116 subjects, or 2PR01 patients.

The FDA's Assessment:

FDA generally agrees with the discussion above regarding adverse events of special interest. In addition to the events, above, FDA considered neurologic events including pain, neuropathy, and neurological disorders of the eye as events of special interest given the mechanism of action of naxitamab.

Note that the Applicant uses the term “infusion-related” to indicate events which occurred on the same day as an infusion of naxitamab. In some cases the Applicant has reported “treatment-related” events, whereas FDA considers all treatment-emergent events in its analysis. In cases where the incidence of an adverse event differs in the FDA analysis based on presentation of only related events, or for other reasons, the incidence will be described below. FDA considered anaphylaxis and angioedema, bronchospasm potentially associated with hypoxia, stridor, and hypotension as components of infusion-related reactions or hypersensitivity, which may be clinically indistinguishable.

Infusion-Related Reactions

Infusion-related reactions were very common in patients in the safety population. The Applicant did not provide a pooled term definition of infusion-related reactions, but described manifestations of infusion reactions separately. FDA performed a pooled term analysis including the following terms: hypotension, bronchospasm, flushing, wheezing, stridor, urticaria, dyspnea, pyrexia, infusion related reaction, face edema, swelling face, orbital edema, periorbital edema, lip edema, lip swelling, mouth edema, tongue edema, swollen tongue, mouth swelling, angioedema, respiratory tract edema, chills, hypoxia, pruritis, rash macular, rash maculo-papular, rash erythematous, rash, and respiratory distress. The analysis was restricted to events which occurred the day of the infusion of naxitamab or the day following an infusion. The intent of the analysis is to capture events within 24 hours; because of the limited number of events across studies which had recorded adverse event start times, the analysis

{DANYELZA, naxitamab-gqgk}

included events which occurred at any time on the day following the infusion. In Trial 12-230, among patients who received the RP2D (n=72), 94% of patients experienced an infusion reaction based on this analysis with 32% experiencing a Grade 3 – 4 infusion reaction; of these there was one Grade 4 event of hypotension (1.4%). Infusion reactions occurred in Cycles 1 – 7 (median cycle 1). Serious events (n=12) included hypotension and pyrexia, and occurred during Cycles 1 – 4. Grade 3 – 4 events (n=34) occurred during Cycles 1 – 7 and 56% of events occurred during Cycle 1. Six patients (8.3%) had an infusion interrupted for an infusion-related reaction based on the retrospective review described earlier in the review.

In Trial 201, 100% of patients experienced an event meeting this definition and 68% of patients experienced a Grade 3 event; there were no Grade 4 infusion reactions as defined by the pooled term. The incidence of components of infusion-related reactions will be described separately below. Any Grade infusion reaction occurred in cycles 1 – 8 (median cycle 3), and occurred with any dose of naxitamab during a cycle (1 – 3); 48% of events occurred with the first dose of naxitamab of a cycle. Grade 3 events (n=128) occurred during cycles 1 – 7 (median cycle 2). Thirty-three percent of Grade 3 events occurred during cycle 1 and 58% occurred during the first infusion of a cycle. Twenty patients (80%) had an infusion interrupted based on an infusion-related reaction; 80% of patients required an infusion rate decrease for an event of infusion-related reaction. Approximately 50% of events had a the time of onset of infusion reaction recorded. Of these events, the median time to onset was 0.34 hours or 20 minutes following initiation of the infusion (range: 1 hour post initiation of the infusion to 16.5 hours after the infusion). Eighty-five percent of infusion reactions with recorded start and end times started within 30 minutes of initiation of infusion.

Reviewer note: Two events were reported with a start time prior to the initiation of infusion of naxitamab, and including pyrexia and urticaria. One is assessed as related to naxitamab. This reviewer suggests that an error in recording start time of either AE or infusion may explain the occurrence of an AE assessed as related to naxitamab occurring before the initiation of the infusion.

The Applicant provided a review of serious grouped-term infusion reactions and evaluated for patients who required ICU admission. One patient in Trial 12-230 was reported as requiring vasopressor support for an infusion reaction. Per review of the narratives, several patients required admission to the intensive care unit (PICU) for monitoring. Seven patients with terms meeting this pooled term definition of infusion reactions were admitted to the ICU although only three were assessed as probably related to naxitamab. Other events were suspicious for infection or postoperative hypotension; this reviewer agrees with this assessment based on the narratives.

{DANYELZA, naxitamab-gqgk}

One patient with Grade 4 hypotension required use of vasopressor support; although this event occurred within the time frame evaluated for infusion related reactions, the event occurred the day following the infusion and the narrative suggests that this event was consistent with sepsis, supported by a positive blood culture (*Staphylococcus aureus*).

According to the Applicant's analysis, 92% of patients with an event of infusion-related reaction (grouped term) required concomitant fluid administration. The analysis in Trial 12-230 was limited by incomplete information on concomitant medications for patients outside the primary efficacy analysis set and included 14.6% of 41 patients who received fluid for a TEAE of infusion-related reaction.

Pre-medication administered to patients in the safety population was variable. In Trial 12-230, the protocol suggested premedication with analgesics and antihistamines but did not require pre-medication. The protocol for Trial 201 contained specific instructions including the following:

- Gabapentin and oxycodone for pain, with IV opioids as needed
- Corticosteroids for all patients at the first infusion in the first cycle and in the following circumstances:
 - o At the first infusion in the following cycle if the patients had a Grade 3 bronchospasm/anaphylaxis at the last cycles first infusion
 - o At the following naxitamab infusion if the patients had a Grade 3 bronchospasm/anaphylaxis at the last infusion
 - o At the investigator's discretion when infusion related reactions are not satisfiable controlled by the other premedications.
- Antipyretics (acetaminophen/paracetamol)
- Antihistamines
- H2 antagonist
- Antiemetics
- Anxiolytics, if applicable

The requirement for administration of corticosteroids for all patients prior to the first dose was implemented soon before the data cut-off for the NDA and is not reflected in the premedication that was actually administered in the safety analysis set for Trial 201. While 100% of patients received antihistamines and antipyretics, and 91 – 100% received H2 antagonists for all infusions in Cycle 1 (n=23 – 25), only 24% of patients received corticosteroids for infusion 1 of cycle 1. The Applicant stated that the change in the protocol was implemented given the high rate of bronchospasm observed in this trial (76% all Grades, 28% Grade 3 -4).

{DANYELZA, naxitamab-gqgk}

In Trial 12-230, collection of concomitant medication data was limited to patients in the Applicant's efficacy analysis set (n=45); among these patients, only one patient received corticosteroids prior to the first dose in Cycle 1 and only one other corticosteroid pre-medication administration (for infusion 3 of Cycle 2) is recorded for any patient. However, rates of administration of antihistamines, H2 antagonists and antipyretics for all infusions (infusions 1 – 3, Cycles 1 – 13) ranged from 80 – 100%.

Reviewer note: Although the safety dataset does not reflect universal administration of corticosteroids in Cycle 1, the reviewer agrees that since this action was taken for safety reasons and given the prevalence and severity of infusion reactions, corticosteroid administration prior to naxitamab should be advised for all patients in Cycle 1 in the product label, as well as in the circumstances outlined in the study protocol.

In Trial 201, there were 101 Grade 3 - 4 AEs in the grouped term analysis where IRR. For 31 events, there was no action recorded as being taken with respect to naxitamab, including Grade 3 hypotension (6 patients), bronchospasm, hypoxia, stridor, and respiratory tract edema. However, there were 98 events of Grade 3 or greater AES which did have an action taken, including 60 events of hypotension in 14 patients. Study drug was interrupted in 58/60 events of hypotension which had an action taken with naxitamab.

Reviewer note: See discussion of management of hypotension below. This reviewer does not agree with the sponsor's approach to management of hypotension.

Respiratory Manifestations of Infusion Reactions

Although there were no events of bronchospasm in Trial 12-230 or Trial 201 which were deemed serious, there were serious events associated with respiratory symptoms related to the infusion, including a patient with Grade 3 hypoxia and hypotension ((b) (6)), a patient with pneumonia, dyspnea and hypoxia ((b) (6)), and respiratory distress ((b) (6)).

In addition, among patients who received the RP2D of naxitamab, 21% of patients in 12-203 experienced stridor, and 15% of patients had Grade 3 stridor. All but one event occurred on the same day as an infusion of naxitamab. Twenty-two percent of patients experienced bronchospasm and 21% of patients experienced dyspnea. These terms are included in the pooled term for infusion-related reactions described above.

As described below, the protocol for Trial 201 contained required dose modifications for patients with Grade 2 or greater bronchospasm with hypoxia.

- Grade 2 bronchospasm: Reduce infusion to 50% of prior rate, which may be resumed if bronchospasm resolves to Grade ≤1.

{DANYELZA, naxitamab-gqgk}

- Grade ≥ 3 bronchospasm with hypoxia: pause naxitamab infusion. If patient recovers from hypoxia (bronchospasm Grade ≤ 2), resume infusion at 50% of infusion rate, and may be increased if bronchospasm Grade ≤ 1 .

Instructions regarding administration of beta2-adrenergic receptor agonist nebulizers, racemic epinephrine inhalation solution, IV antihistamine and IV corticosteroids were also provided in the protocol but not described in detail in this review.

The product label includes instructions for dose modifications for infusion reactions as a combined term encompassing bronchospasm, hypotension, etc., and are similar to the instructions from the Trial 201 protocol described above.

Hypotension

Hypotension is included in the pooled term of infusion-related reactions above. FDA notes that the incidence of Grade ≥ 3 hypotension was 7% in Trial 12-230 among patients who received the RP2D, with 11% of patients experiencing an SAE of hypotension. In Trial 201, 60% of patients experienced Grade ≥ 3 hypotension. This may be due to the subjectivity of grading hypotension in CTCAE v4 as described below:

- Grade 2: non-urgent medical intervention indicated
- Grade 3: medical intervention or hospitalization indicated
- Grade 4: life-threatening and urgent intervention indicated.

The toxicity Grade assigned depends upon the healthcare provider's definition of "non-urgent;" this reviewer would argue that infusion-associated hypotension would typically prompt urgent medical intervention (such as stopping or slowing an infusion or providing fluid support if needed). Therefore the difference in incidence of Grade ≥ 3 hypotension between the two primary studies may not represent a true difference in incidence but rather differing interpretation of the grading system.

As indicated in Section 11, (b) (4)
FDA revised the product label to include a Warning for serious infusion-related reactions, which includes hypotension.

The protocol for Trial 201 included instructions for management of hypotension. Infusion interruption or infusion rate reduction was not required for Grade 2 hypotension. Instructions are summarized below.

- Grade 3 hypotension without other symptoms:
 - o Decrease in the rate of naxitamab by 50%; if patient stabilizes, consider resuming to normal infusion speed based on clinical judgement
- Grade 3 hypotension with other symptoms such as bradycardia, hypoxia, 'not adequately

{DANYELZA, naxitamab-gqgk}

responding' or Grade hypotension:

- o Pause naxitamab infusion. If patient warm and well-perfused, treat hypotension, may resume naxitamab infusion at 50% of prior rate upon resolution to Grade ≤ 2 .
- o If patient not warm and well-perfused, inadequate response to fluid resuscitation, consider naloxone, epinephrine IV/IM. May resume naxitamab infusion at 50% of prior rate upon resolution to Grade ≤ 2 .
- o If patient continues to be hypotensive/difficult to arouse or Grade 3 hypotension recurs, stop naxitamab infusion.
- o Subsequent infusions initiated at discretion of investigator at 50% of rate of infusion prior to the event, and investigator should consider adjustments of pre-medication.

Reviewer note: In the opinion of this reviewer,

(b) (4)

is not adequately conservative. FDA has proposed a management strategy for interruption or rate reduction of naxitamab in the event of infusion-related reactions as a group

(b) (4)

and proposes to require rate reduction in patients with Grade 2 IRRs, with interruption in patients with Grade 3 IRRs and permanent discontinuation in patients with Grade 4 IRRs or Grade 3 IRRs that do not respond to intervention (see naxitamab product label for details).

Anaphylaxis and Angioedema

Three patients on Trial 201 (12%) and two patients enrolled on Trial 12-203 at any dose (n=117) experienced serious events of anaphylaxis. One event in Trial 201 was attributed to GM-CSF. A challenge in interpretation of infusion related reactions is that infusion reactions with monoclonal antibodies may overlap with anaphylaxis and may be indistinguishable. (LaCasce, 2020)

The majority of events of anaphylaxis (excluding the event attributed to GM-CSF) resulted in discontinuation of naxitamab. However, in response to an event of Grade 3 anaphylaxis in Study 201 (patient (b) (6)), naxitamab was not discontinued. The patient received the remainder of the first cycle of naxitamab, but experienced Grade 4 anaphylaxis during the first dose of naxitamab during cycle 2.

This reviewer notes that CTCAE v 4.0 defines Grade 3 and 4 anaphylaxis as follows:

- *Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension*

{DANYELZA, naxitamab-gqgk}

- *Grade 4: Life-threatening consequences; urgent intervention indicated*

The reviewer notes that untreated anaphylaxis of any Grade is generally life-threatening and thus there is potential that different providers would Grade the same event differently. This reviewer considers that all anaphylactic reactions should prompt permanent discontinuation of naxitamab given the serious risk of life-threatening reactions, (b) (4)

The case of patient (b) (6) (Study 201) also illustrates the potential need for extended monitoring following infusion for patients treated for infusion-related reactions. This patient experienced the event of Grade 3 anaphylaxis previously referenced three hours after infusion. He had received diphenhydramine for lip and tongue swelling at the end of infusion. (b) (4)

hence, FDA recommended that product labeling include instructions for close monitoring for signs and symptoms of an infusion reaction during and for at least 2 hours following completion of the naxitamab infusion. Narratives from Study 12-230 do not all include the exact time of onset of signs or symptoms associated with infusion reactions or anaphylaxis, whereas narratives from Study 201 collected this information in approximately 50% of cases of infusion reactions. Onset of hypotension or bronchospasm was generally during the infusion or at the end of the infusion. Since the majority of the safety data is derived from Study 12-230, an assessment of the exact timing of onset of infusion reactions and anaphylaxis is limited.

Hypertension

FDA agrees with the description of the incidence of hypertension above. In Trial 12-230, there were 12 SAEs of hypertension (10.2%), and four led to discontinuation of naxitamab. In addition, two of these (which led to discontinuation) had MRI findings potentially consistent with PRES, as described below. Among patients who received the RP2D of naxitamab (n=72), 10 (14%) had an SAE of hypertension.

This reviewer notes that there are limitations to the CTCAE v 4.0 grading of hypertension for children; CTCAE v 5.0 has revised the definition for pediatric patients. Normal blood pressure for children varies and norms are classified based on gender, height percentile, and age. CTCAE v 4.0 provides the following guidance for grading hypertension in children:

- Grade 1: No specific mention of children; for adults, prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)
- Grade 2: Recurrent or persistent (≥ 24 hrs) BP $>$ ULN; monotherapy indicated

{DANYELZA, naxitamab-gqgk}

- Grade 3: Stage 2 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated. Pediatric: same as adult.
- Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated. Pediatric: Same as adult.

In practice, for children < 13 years of age, Stage 2 hypertension is classified as systolic and diastolic blood pressures ≥ 95 th percentiles + 12mm Hg, or $\geq 140/90$ mm Hg (whichever is lower), and for children 13 years and older, this is defined as $\geq 140/90$ mm Hg.

Therefore this reviewer considers that the severity of some events captured as "Grade 2" in patients who had systolic blood pressures between 140 - 160 mm Hg underestimates the severity of hypertension when considering the patient's age-based norms. This should be considered when interpreting the data describing this toxicity.

Two events of hypertension not reported as PRES in Trial 12-230 had MRI findings potentially consistent with PRES, as described in the narratives below:

Patient (b) (6): This is a 3 year old with stage 4 neuroblastoma who experienced Grade 2 hypertension and Grade 1 urinary retention during his first cycle of naxitamab (3.0 mg/kg/dose). He received naxitamab as an inpatient for social reasons. He had intermittent hypertension starting after his first dose (145/96) which continued past the administration of the third dose of naxitamab. An MRI done two days after the administration of the last dose of naxitamab showed 'diffuse white matter lesions that could be suggestive of PRES.' He was discharged 10 days following completion of naxitamab. Naxitamab was discontinued because of the event.

Patient (b) (6): This is a three year old boy originally diagnosed with Stage 3 neuroblastoma who experienced Grade 3 hypertension the day following infusion of naxitamab (3.0 mg/kg/dose). He was evaluated in urgent care for a routine blood pressure check and had a BP of 130/88 while asleep (99th percentile for age 112/71). He had been experiencing nausea at home but had no neurologic changes concerning for PRES. He was admitted for blood pressure and nausea control and was discharged the following day, but follow-up the subsequent day (3 days post infusion) demonstrated worsened hypertension (199/78). The family was given a prescription for enalapril to be given as needed. During his second cycle of naxitamab, he experienced a serious AE of fever and hypertension. One day after his third dose of naxitamab he was admitted due to persistent fever and was hypertensive on exam. MRI showed suspicion for subtle early PRES. Naxitamab was discontinued due to the event.

{DANYELZA, naxitamab-gqgk}

For the 7 events of hypertension for which a start time was recorded in Trial 201, the median time to onset was 1.4 hours (range 0.4 to 3.9 hours) and median duration was 2.2 hours (range 0.5 hours to 7 days). Events of hypertension were more likely to be recorded on the 3rd infusion of naxitamab of a cycle. For all events of hypertension (regardless of whether an exact start time was recorded) in Trial 201 (n=25), events occurred on a median of day 1, with day 1 being the day of the infusion (range 1 – 2) relative to an infusion of naxitamab.

In Trial 12-230, event start time was rarely recorded and the analysis was conducted in days. Events occurred from days 1 – 9 relative to an infusion of naxitamab (median day 1) and the majority of events occurred the day of or the day following an infusion (31/40, or 78%). The median duration in Trial 12-230 was 1 day (range 1 to 29 days). Among Grade 3 events, the median duration was 3.0 days (range 1 to 5 days).

Reviewer note: The timing of onset of hypertension appears to have a wider range in Trial 12-230. The reviewer hypothesizes that greater awareness of this adverse reaction may have led to additional monitoring and earlier diagnosis; however, it may also be a result of the small safety database for Trial 201.

Eight patients (11%) in the safety population in Trial 12-230 and 7 patients (25%) in Trial 201 received antihypertensive medications.

Neurotoxicity including Pain, Neuropathy and Neurological Disorders of the Eye

Pain

Pain was present in nearly all patients in the safety populations of both Trials 201 and 12-230. In Trial 201, 100% of patients had any Grade of pain and 72% of patients had Grade ≥ 3 pain. Events of pain lasted 0 – 28 days with a median of 0 days (indicating the event resolved the same day). There were 345 events in total, and all but 4 occurred on the day of an infusion of naxitamab. Among events that had a recorded start time in Trial 201, the median time to onset was 0.18 hours or approximately 11 minutes (range 0 to 22 hours) following initiation of the infusion; for Grade 3 events the median time to onset was also 0.18 hours or 11 minutes (range 0.05 hours to 1 hour). Events of pain lasted a median of 2.3 hours (range 0.08 to 249 hours or 10 days). Among Grade 3 events, the median duration was 2.2 hours (range 0.08 to 60 hours or 2.5 days).

{DANYELZA, naxitamab-gqgk}

In Trial 12-230, 94% of patients treated at the recommended phase 2 dose had any Grade of pain and no patients had an event of Grade 3 or greater pain. Events of pain lasted 0 – 29 days with a median of 0 days. There were 395 events total and 23 did not occur on the day of an infusion, occurring up to 18 days following infusion.

A grouped term analysis of pain included the following terms: pain, abdominal pain, pain in extremity, bone pain, neck pain, back pain, non-cardiac chest pain, flank pain, and musculoskeletal pain. In Trial 201, 100% of patients had any Grade of pain and 72% of patients had Grade ≥ 3 pain. Based on an analysis of all events performed in days, events of pain lasted 0 – 62 days with a median of 0 days (indicating the event resolved the same day). One patient in Trial 201 had a dose interruption and one had a dose decrease due to an event of pain; upon clarification from the study site, the dose of naxitamab was not decreased, but the patient was given medication for pain.

Based on an analysis of the subset of events with recorded start and end times, grouped term events of pain lasted a median of 1.9 hours (range 5 minutes – 2 days).

In Trial 12-230, 94% of patients treated at the recommended phase 2 dose had any Grade of pain and 2.8% of patients had an event of Grade 3 or greater pain. Events of pain lasted 0 – 29 days with a median of 0 days.

Trial 201 advised administration of gabapentin starting on Day -4 of each cycle and continuing through Day 7. Ninety-two percent (92%) of patients received gabapentin premedication in Trial 201. Both study protocols advised premedication with opioids prior to administration of naxitamab. The protocol for Trial 201 advises administration of oxycodone 45 – 60 minutes prior to naxitamab.

Reviewer note: Given the prevalence of pain with naxitamab infusion, the product label will include guidance on pre-medication for pain.

Neurological Disorders of the Eye

FDA performed a pooled term analysis to evaluate neurological disorders of the eye. The pooled term "eye disorders" excluded events with terms related to infection, swelling, hemorrhage and could be related to neurologic disorders of the eye and included the terms photophobia, pupils unequal, vision blurred, accommodation disorder, optic nerve disorder, mydriasis, and visual impairment.

In Trial 12-330, among the 117 patients treated with naxitamab at any dose, there were 32 events of neurological disorders of the eye in 19 patients (16%). Seventeen events were

{DANYELZA, naxitamab-gqgk}

assessed as definitely, possibly, or probably related to naxitamab. There were no serious events and all were Grade 1 - 2. All events resolved (resolution occurred on a median of day 1). In the subset of patients who received the RP2D (n=72), 19% of patients experienced event meeting on the terms listed above; there were no Grade 3 – 4 events. Events occurred from days 1 – 29 relative to an infusion (median day 1, or the day of infusion). All events resolved and lasted 0 – 21 days (median 1 day).

In Trial 201, 24% of patients had an event in the pooled term analysis (including terms mydriasis, pupils unequal, vision blurred). Events occurred a range of 1 - 18 days relative to most recent infusion (median 1 day) during cycles 1 - 4 (median cycle 2). Two of 9 events (mydriasis) were ongoing at data cut-off; of events that resolved, the range of duration of events was 0 - 84 days with median of 17 days. All were grades 1 - 2 and none were serious. The Applicant provided follow-up information regarding the ongoing cases of Grade 2 mydriasis; these two cases were not resolved as of the data cut-off for the 120-day safety update with reported symptoms of photophobia. In addition, two other cases of mydriasis with onset after the DCO for the original application were provided; one of these events was reported as ongoing. The ongoing events have durations of approximately 17 months, 6 months, and 6 weeks.

This reviewer notes that mydriasis does not have a dedicated CTCAE term according to v 4.03, but Grade 2 eye disorders are defined as follows: “Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.”

Based on the prolonged nature of these events of mydriasis with accompanying symptoms, FDA considered that intervention with respect to naxitamab administration may be indicated in some instances including those with visual impairment. The final recommendations are reflected in Section 2 of the product label.

Neuropathy

A grouped term analysis was performed for neuropathy including the following terms: peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, neuralgia. In Trial 12-230, 25% of 72 patients who received the RP2D experienced an event. Seventeen of 34 (50%) events occurred on the day of an infusion and all but two events occurred within 1 week of infusion (range 1 - 25 days, median 1.5). Events lasted less than one day to 22 days with a median duration of median less than one day (the event resolved later the same day). All events were Grade 1 – 2 and there were no serious events.

In Trial 201, 32% of patients had an event of neuropathy as defined by the grouped term analysis with terms listed above. Events occurred on a median of day 1 relative to the infusion

{DANYELZA, naxitamab-gqgk}

(the day of infusion), with a range of 1 - 17 days from the infusion. Events occurred during cycles 1 – 5 (median cycle 2). Three events were not resolved per the dataset; a request for follow-up data from the sponsor indicated that two of these events had resolved, with the remaining event of Grade 1 peripheral neuropathy listed as ongoing (event duration as of August 2020 was approximately 16 months). For those that resolved, median duration was 5.5 days (range 0 - 22 days). All events were Grade 1 – 2 and there were no serious events.

The study protocol for Trial 201 required discontinuation of naxitamab in the instance of Grade 4 sensory neuropathy or Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks. FDA considered that a lower threshold would be indicated for discontinuation in the event of motor neuropathy given the interference with daily activities. The final recommendations are reflected in Section 2 of the product label.

Urinary Retention

Urinary retention was investigated as a potential safety signal. Among patients treated on Trial 12-230 at any dose of naxitamab, three patients had serious events of urinary retention or urine output decreased. One serious event was deemed unlikely related to naxitamab by this reviewer due to potential obstruction with ureteral stent. Two cases appeared potentially related though confounded by 1) baseline urinary incontinence and "disease-related neurologic defects" and 2) concomitant medication (sedation, opioids). The second case is discussed below:

- Patient (b) (6) experienced a serious adverse event of Grade 1 urinary retention which lasted 10 days. The patient was sedated for bone marrows and CT and MIBG scans on the day the event started, and the event resolved 5 days after last administration of opioids.

There were two non-serious cases of prolonged urinary retention in Trial 12-230 which occurred in a single patient.

- Patient (b) (6) had two events of urinary retention lasting 5 and 24 days. The event lasting 5 days in duration resolved on the third day after opioids were discontinued and did not require hospitalization. The event recorded as lasting 24 days had no source documentation available in the electronic medical record and thus a narrative could not be provided.

In Trial 12-230 among patients treated at any dose, 8 patients (6.8%)) had 11 events of urinary retention, with no Grade 3 – 4 events. The events occurred on days 1 - 6 relative to the most recent infusion of naxitamab, with a median of 1 day. All events were reported as resolved with

{DANYELZA, naxitamab-gqgk}

a duration 0 - 24 days (median 3 days). In 12-230 among patients who received the RP2D, 3 patients experienced 5 events of urinary retention. All events occurred on the day of infusion and all but one event occurred during cycle 1 (remaining event during cycle 2). All events resolved, and lasted 0 - 24 days (median 5 days). One event was serious. All events were Grade 1 - 2. In Trial 201, 1 patient had 3 events of urinary retention. All occurred on the same day as an infusion and resolved the same day.

FDA considered that events of urinary retention that do not resolve for a prolonged period after discontinuation of opioids should prompt discontinuation of naxitamab. The final recommendations are described in Section 2 of the product label.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees this section is not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Carcinogenicity studies have not been conducted with naxitamab.

The FDA's Assessment:

FDA agrees and has no further comment.

{DANYELZA, naxitamab-gqgk}

Human Reproduction and Pregnancy

The Applicant's Position:

Pregnancy

No studies of naxitamab in pregnant women or dedicated reproductive toxicity studies in animals have been performed.

Lactation

No studies have been performed to evaluate the risk potential of naxitamab in lactating and breastfeeding patients.

Females and Males of Reproductive Potential

In animal toxicity studies, treatment with naxitamab did not induce any morphological changes in male and female reproductive organs. The potential for treatment with naxitamab to impair reproductive potential has not been studied in humans.

The FDA's Assessment:

Refer to section 5.5.4 for a discussion of animal toxicity studies. FDA does not have additional comments.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

The vast majority of patients for the indicated use of naxitamab are pediatric. The safety and effectiveness of naxitamab have been established in pediatric patients with high-risk neuroblastoma based on results from clinical trials in patients aged 12 months and older.

The FDA's Assessment:

The effect of naxitamab on growth in pediatric patients has not been characterized in this application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

No cases of overdose have been reported. Naxitamab will be administered by qualified

{DANYELZA, naxitamab-gqgk}

healthcare personnel in a hospital setting. There is no known potential for abuse potential for naxitamab. Naxitamab has a fairly long half-life (8.2 days), thus signs or symptoms of withdrawal or rebound are not expected.

The FDA's Assessment:

FDA agrees that there is no known potential for abuse and is not aware of any cases of overdose.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA has no further comment.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor the safety of naxitamab in combination with GM-CSF.

The FDA's Assessment:

Based on the occurrence of severe infusion reactions, FDA determined that a black box warning was necessary to advise healthcare providers of this risk and need for careful monitoring and management. The safety experience with this product represented in this application is largely derived from a single center. Additional safety data to characterize the risk of severe infusion reactions in a multicenter setting will be requested from the ongoing multicenter trial (201) as a postmarketing requirement.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The assessment of safety is supported by data from four clinical trials and data collected for patients treated under compassionate use.

Common treatment-related events were mainly Grades 1 or 2 and included pain, abdominal pain, pain in extremity, pyrexia, urticaria, pruritus, nausea, vomiting, hypotension, hypertension, and bronchospasm. More than 75% of treatment-related events were infusion related.

Grade 3+ treatment-related events of importance included anaphylaxis, angioedema, hypotension, bronchospasm, and hypertension. The incidence of treatment-related SAEs across trials was comparable and below 30%. No deaths occurred.

On the basis of its mechanism of action, naxitamab may cause severe pain, which is expected to occur for many patients receiving naxitamab. Pain was the most frequently reported adverse reaction, reported by almost all subjects. These events were associated with naxitamab infusion and resolved quickly after the infusion was complete. In the naxitamab clinical program, pain was managed by premedication. Gabapentin was administered at home starting 3 days before the day of naxitamab infusion. On the day of infusion, opioids were given before and during infusion to manage pain. Generally, the highest scores for pain were reported during the 30-minute naxitamab infusion, with pain subsiding before hospital discharge.

Infusion reactions

Naxitamab has been shown to cause infusion reactions, including anaphylaxis, bronchospasm, skin reactions, oedema, and hypotension. Infusion reactions generally occurred soon after initiating naxitamab and may last for up to 2 hours after the infusion. Infusion reactions are most frequent during first infusion in each cycle. The onset of hypotension and bronchospasm generally occurred during naxitamab infusion. Hypotension and bronchospasm tend to be more frequent and more severe at the first infusion of a cycle and worst at the first infusion of the first cycle. In the clinical development program, subjects were premedicated with antihistamines, antipyretics, and corticosteroids to minimize these risks. Furthermore, mitigations were in place, including reduction of infusion speed and ability to give concomitant medications, such as nebulizer with beta2-adrenergic receptor agonist; S2 inhalation; and additional antihistamines, antipyretics, and/or corticosteroids.

{DANYELZA, naxitamab-gqgk}

Anaphylaxis can be a serious reaction to any monoclonal antibody therapy. To mitigate the risk of anaphylaxis, administration of naxitamab will be contraindicated for any patient that has had an anaphylactic reaction (CTCAE Grade 4) to another anti-GD2 therapeutic. Part of the premedication regimen for naxitamab is the administration of corticosteroids and antihistamines to aid in the prevention of severe immune reactions, and guidance is provided to physicians to aid in the management of anaphylactic reactions in the product information. Naxitamab can be administered in an out-patient setting, but must be administered in a facility by a health care professional with immediate access to emergency equipment and appropriate medical support to manage severe adverse reactions, if they occur.

Hypertension

Naxitamab may cause severe hypertension. Not all hypertension started on a day of a naxitamab infusion, but occurred later. For treatment-related hypertension occurring at the day of naxitamab infusion, 12.0% of SAF subjects reported infusion-related hypertension. In Trial 12-230, about half of the serious hypertensions started on the day of or 1 calendar day after Cycle 1, Infusion 3, and other serious hypertension events started at earlier infusions in Cycle 1. PRES was observed in two subjects, but only one subject discontinued treatment. Mitigations for hypertension are defined in the label, including additional BP measurements, (b) (4)

Subpopulations

No safety concerns were raised based on subgroup analyses. Safety data demonstrated patterns of events consistent with those reported for the overall population.

Laboratory findings

In the naxitamab clinical development program, there were no signs of nephrotoxicity, drug-induced liver injury, or myelosuppression.

In conclusion, the safety profile of naxitamab was well characterized in the clinical development program of naxitamab in combination with GM-CSF for patients with high-risk refractory or relapsed neuroblastoma in bone and/or bone marrow.

Events of pain, hypotension, bronchospasm, and hypertension (including CTCAE Grade 3 and above) are expected to occur for many patients receiving naxitamab, based on the clinical data. To minimize or mitigate these events, guidance for the management of these is provided in the label.

{DANYELZA, naxitamab-gqgk}

Naxitamab treatment has proved tolerable for the majority of subjects as shown by the relatively small number of withdrawals because of adverse events. Most adverse reactions are limited to the day of infusion, and the effects of the treatment have been manageable through premedication regimens, analgesic administration during infusions, and careful monitoring of patients during and in the period after infusion.

The FDA's Assessment:

The safety of naxitamab in combination with GM-CSF was evaluated in a subpopulation of patients with high-risk neuroblastoma in bone or bone marrow and had relapsed or refractory disease, or were in complete remission, from two open-label, single arm studies, Study 201 (n=25) and Study 12-230 (n=72). In both studies, patients received naxitamab as three separate intravenous infusions of 3 mg/kg (day 1,3 and 5) in first week of a pre-planned 4-week cycle. Patients also received GM-CSF subcutaneously at 250 µg/m²/day on days -4 to 0 and at 500 µg/m²/day on Days 1 to 5.

During Trials 201 and 12-230 as of the data cut-off for the application, there were no deaths. Cumulative safety data indicated that SAEs occurred in 32% of patients in Trial 201 and 40% of patients in Trial 12-230. Serious adverse reactions in > 5% of patients in Trial 201 included anaphylactic reaction (12%) and pain (8%); in Trial 12-230 SAEs in >5% of patients included hypertension (14%), hypotension (11%), and pyrexia (8%).

Naxitamab can cause serious infusion-related reactions and neurologic toxicity. Given the potential severity of these adverse reactions and the occurrence of infusion related reactions and pain in most patients in either trial, a boxed warning was included in the product label.

Serious infusion reactions required urgent intervention including fluid resuscitation, administration of bronchodilators and corticosteroids, intensive care unit admission, infusion rate reduction or interruption of naxitamab infusion. Components of these infusion reactions included hypotension, bronchospasm, hypoxia, wheezing, and stridor. Infusion reactions of any Grade occurred in 100% of patients in Trial 201 and 94% of patients in Trial 12-230. In Study 201, 68% of patients in Trial 201 experienced a Grade 3 infusion reaction; while in Study 12-230, 29% of patients experienced a Grade 3 infusion reaction and 1.4% experienced a Grade 4 infusion reaction. One patient in Study 12-230 (1.4%) experienced a cardiac arrest 1.5 hours following completion of naxitamab infusion. Anaphylaxis occurred in 12% of patients in Study 201. The product label contains detailed instructions for pre-medications as well as instructions for slowing, interrupting or permanently discontinuing naxitamab infusions based on the severity of the adverse reaction.

{DANYELZA, naxitamab-gqgk}

Neurotoxicity experienced in patients receiving naxitamab included pain, peripheral neuropathy, neurological disorders of the eye, transverse myelitis, and PRES/RPLS. Pain, including abdominal pain, bone pain, neck pain, and extremity pain, occurred in 100% of patients in Study 201 and 94% of patients in Study 12-230. Grade 3 pain occurred in 72% of patients in Study 201.

Peripheral neuropathy including peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, and neuralgia occurred in 32% of patients in Trial 201 and in 24% of patients in Trial 12-230. Neurological disorders of the eye occurred in 19% of patients in Trial 12-230 and 24% of patients in Trial 201; 8% of patients in Study 201 experienced an event that had not resolved based on the data cut-off of the 120-day safety update. Urinary retention occurred in 4% of patients in Trial 201 and Trial 12-230 and in some patients persisted beyond discontinuation of opioids. Transverse myelitis occurred in a patient receiving naxitamab outside of a clinical study. RPLS occurred in 2 (2.8%) patients in Trial 12-230. The product label describes neurotoxicity as a warning, and provides guidance on dose modifications or discontinuations

Hypertension occurred in 44% of patients in Study 201 and 28% of patients in Study 12-230 who received naxitamab. Grade 3 hypertension occurred in 4% of patients in Trial 201 and 7% of patients in Trial 12-230 and led to permanent discontinuation of naxitamab in some patients. In both studies, most events occurred on the day of a naxitamab infusion and occurred up to 9 days from an infusion. The product label describes this risk and the need for extended monitoring of blood pressure.

The most common adverse reactions in Trial 201 ($\geq 25\%$) were pain, infusion-related reaction, tachycardia, cough, vomiting, diarrhea, nausea, hypertension, peripheral neuropathy, urticaria, pyrexia, headache, edema, sinus tachycardia, and fatigue. The most common grade 3 or 4 laboratory abnormalities ($\geq 5\%$) were decreased neutrophils, decreased lymphocytes, decreased platelet count, increased alanine aminotransferase and decreased potassium.

The most common adverse reactions ($\geq 25\%$) in Trial 12-230 were infusion-related reaction, pain, vomiting, cough, nausea, diarrhea, decreased appetite, sinus tachycardia, fatigue, erythema multiforme, hypertension, injection site reaction, anxiety, irritability, and localized edema. The most common grade 3 or 4 laboratory abnormalities ($\geq 5\%$) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased platelet count, decreased potassium, increased alanine aminotransferase, decreased glucose, decreased sodium, decreased albumin, and decreased phosphate.

{DANYELZA, naxitamab-gqgk}

Clinically relevant adverse reactions in $\leq 10\%$ of patients who received naxitamab with GM-CSF in either study included apnea, hypopnea, generalized edema, peripheral edema, and device related infection.. Events of apnea, hypopnea, unresponsiveness and somnolence also occurred in some patients and may be related to concomitant administration of opioids or to co-occurring events of severe infusion reactions, such as severe hypotension.

The safety population included patients ages 1 to 24 years of age across both trials, with a median age of 5 years in both trials. Although relatively few young adult patients and very young patients (2 years of age or younger) were enrolled, exploratory analyses of safety trends did not demonstrate a significant difference in safety across groups.

Overall, the risks associated with naxitamab appear acceptable in the setting of patients with relapsed or refractory neuroblastoma who have no approved therapies. Naxitamab is expected to be administered in infusion centers with intensive monitoring and the ability to quickly respond to events such as severe infusion reactions. In addition, the existence of previously approved products in the US (dinutuximab) with a similar mechanism of action and toxicity profile means that the majority of pediatric oncologists administering naxitamab will have familiarity with expected toxicities associated with anti-GD2 antibodies. FDA assessed that the communication of risk in the product label required the addition of a boxed warning given the potential severity of the reactions.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were two major statistical issues in the review of this application.

The first statistical review issue was that in Trial 12-230, each patient may have had multiple enrollments in the study. To avoid collinearity in the assessment of response in the same patients over multiple enrollments, only the data from the eligible first enrollment was considered. This limitation to the sample size in addition to the clinical consideration to consider only patients with baseline evaluable disease who initiated at least one infusion of 3.0 mg/kg or greater of naxitamab (as opposed to having completed at least one cycle as proposed by the Applicant) resulted in a final sample size of 38 patients in Trial 12-230.

The second statistical review issue was regarding the follow-up time in Trial 12-230. Given the structure of the assessments for the study reduced the possibility of longer follow-up for DOR, the inference that can be made from the study data is limited. In general, FDA is unable to determine whether the observed results for DOR reflect the actual duration of the treatment effect or whether the results underestimate the duration of response due to censoring. Therefore, both the observed proportion of responders with response ongoing at 6 months (26 weeks) was presented in addition to the Kaplan-Meier estimates .

8.4. Conclusions and Recommendations

The FDA's Assessment:

Patients with relapsed and refractory neuroblastoma in the bone or bone marrow who have demonstrated a response of partial response, minor response, or stable disease to prior therapy represent a population with a serious and life-threatening rare disease for which there is no FDA-approved therapy and no known curative therapy.

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The recommendation for accelerated approval is based on the results from two single-arm, open-label trials.

The trials enrolled patients with relapsed or refractory high risk neuroblastoma in the bone or bone marrow. The primary efficacy population included patients with relapsed or refractory disease in the bone or bone marrow who had demonstrated a response of partial response, minor response or stable disease, to prior therapy, had evaluable disease per central review according to the revised International Neuroblastoma Response Criteria (INRC), and who

{DANYELZA, naxitamab-gqgk}

received at least one dose of naxitamab. The primary efficacy population included 22 patients in Trial 201 and 38 patients in Trial 12-230.

The analysis of efficacy demonstrated a clinically meaningful ORR per independent review with sufficient duration to indicate a clinical benefit in this relapsed and refractory population. It should be noted that patients in both trials were permitted to receive radiation in certain circumstances, though assessment of response excluded sites that received radiation. Patients for whom radiation was administered to the only site of evaluable disease, which applied only to patients in Trial 12-230, were excluded from the efficacy analysis. Patients with a best response of progressive disease to initial therapy or therapy at relapse were excluded from Trial 201 and from the efficacy analysis population in Trial 12-230. Therefore, the indication the review team proposes for approval also excludes these patients.

The confirmed ORR in patients with metastatic, relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a response of stable disease, partial response, or minor response to prior therapy in Trial 201 (n=22) per blinded, independent review was 45% (95% CI: 24%, 68%), with 30% of the 10 responders having observed DOR of 6 months. The primary efficacy analysis in Trial 201 included 4 patients with prior anti-GD2 treatment. One (25%) of these patients demonstrated a response.

The confirmed ORR in patients with metastatic, relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a response of stable disease, partial response, or minor response to prior therapy in Trial 12-230 (n=38) per blinded, independent review according to the revised INRC was 34% (95% CI: 20%, 51%), with 23% of the 13 responders having observed DOR of 6 months. The primary efficacy analysis in Trial 12-230 included 22 patients with prior anti-GD2 treatment. Four (18%) of these patients demonstrated a response (95% CI 5%, 40%). Given the limited number of patients, the point estimate for these results needs to be interpreted with caution; however, the results suggest that naxitamab has some clinical activity in patients with prior anti-GD2 antibody therapy. The difference in ORR between the two trials may be explained by the higher percentage of relapsed patients, who are more heavily pre-treated, in Trial 12-230 (55% vs. 36% in Trial 201).

During the review, the review team considered the impact of a short “wash-out” period between prior systemic therapy and the timing of baseline disease assessments for both studies. FDA considered whether the short time from completion of systemic therapy until the baseline disease assessment could confound the assessment of response to naxitamab. In practice, the urgency to enroll patients, particularly with primary refractory disease who may have demonstrated stable disease, minor response or partial response to prior intensive chemotherapy, onto a clinical trial may render a standard washout period from prior therapy

{DANYELZA, naxitamab-gqgk}

(i.e., at least 4 weeks prior to baseline disease assessment) challenging. Since patients with progressive disease were excluded from the trial, patients with relapsed disease were treated first with other therapy (typically chemotherapy or chemotherapy and immunotherapy) prior to enrollment, thus the concern that the effect of prior therapy is not reflected in the baseline disease assessment (and thus that responses observed in the trial cannot wholly be attributed to naxitamab) is greater in this population. FDA performed a sensitivity analysis removing patients with a short interval (< 2.5 weeks) between systemic therapy and baseline disease assessment, which resulted in similar ORRs in comparison to those noted above in both trials, and also resulted in the exclusion of durable complete responses that the review team did not consider reasonably attributable to prior therapy. FDA's approach was therefore to exclude patients with no washout period between systemic therapy and baseline disease assessments, which applied to one patient in Trial 12-230 as described in the review.

Assessment of duration of response was limited by administration of additional anticancer therapies subsequent to achieving a complete or partial response in patients in both trials. Neither study was designed to include scheduled assessments of response after completion of treatment with naxitamab, and Trial 201 is currently ongoing. Additional clinical data from Trial 201 may provide additional data to inform durability of responses.

Although the two trials supporting efficacy and safety in this application used different manufacturing processes, OBP determined that the products used in each trial were generally comparable, although direct comparability of potency was not possible given differences in potency assays used for each product. Refer to OBP assessment memo, p. 32, for details.

Given the rarity of relapsed or refractory high-risk neuroblastoma and the lack of an approved or standard treatment, a randomized trial may not be feasible. The review team considers that the ORR in the two trials, along with the observed duration of responses, in patients treated with naxitamab is sufficient to establish clinical benefit in the rare group of patients with high risk neuroblastoma. Data from additional patients in this patient population including overall response rate and duration of response, may be required to confirm clinical benefit.

The safety of naxitamab in combination with GM-CSF was evaluated in a subpopulation of 97 patients with high-risk neuroblastoma in bone or bone marrow who had relapsed or refractory disease, or were in complete remission, from the two open-label, single arm studies used to support efficacy, Trials 201 and 12-230; patients in the primary safety population received the recommended phase 2 dose (3 mg/kg/day) of naxitamab intravenously on days 1, 3, and 5 of each cycle and GM-CSF 250 µg/m²/day subcutaneously on Days -4 to 0 and GM-CSF 500 µg/m²/day subcutaneously on Days 1 to 5. Infusion-related reactions and neurotoxicity were prominent and potentially severe safety signals evaluated during the review.

{DANYELZA, naxitamab-gqgk}

Nearly all patients in both studies (100% of patients in Study 201 and 94% of patients in Study 12-230) experienced an infusion reaction, as defined by a pooled term analysis of events as described in Section 8.2.5. In Study 201, 68% of patients experienced a Grade 3 infusion reaction; while in Study 12-230, 32% of patients experienced a Grade 3 infusion reaction and 1.4% experienced a Grade 4 infusion reaction. One patient in Study 12-230 (1.4%) experienced a cardiac arrest 1.5 hours following completion of an infusion of naxitamab. Given the prevalence and severity of infusion-related reactions, as well as the need for careful monitoring and management, IRRs are included as a black box warning in the product label.

Neurotoxicity experienced by patients who received naxitamab included pain, peripheral neuropathy, prolonged urinary retention, transverse myelitis, neurological disorders of the eye, and reversible posterior leukoencephalopathy syndrome. Pain occurred in 100% of patients in Study 201 and 94% of patients in Study 12-230. Grade 3 pain occurred in 72% of patients in Study 201. The USPI advises premedication to treat neuropathic pain. Peripheral neuropathy including sensory neuropathy, motor neuropathy, paresthesia and neuralgia occurred in 32% of patients in Study 201 and in 24% of patients in Study 12-230. Neurological disorders of the eye including mydriasis and blurred vision occurred in 19% of patients in Study 12-230 and 24% of patients in Study 201, and in some cases were prolonged and had not resolved as of the data cut-off for the BLA. Prolonged urinary retention beyond discontinuation of opioids, transverse myelitis, and RPLS were also reported in patients who received naxitamab. Given the severity of these reactions in some patients, the prevalence of events of neurotoxicity, and the need for careful monitoring, neurotoxicity was included as a black box warning in the product label.

Hypotension was a prominent component of infusion-related reactions, but hypertension was also observed in patients who received naxitamab, in some cases associated with RPLS or causing permanent discontinuation of naxitamab. Hypertension occurred in 44% of patients in Study 201 and 28% of patients in Study 12-230 who received naxitamab. Grade 3 hypertension occurred in 4% of patients in Study 201 and 7% of patients in Study 12-230. Hypertension is included as a warning in the product label.

The most common adverse reactions in Studies 201 and 12-230 (> 25% in either study) were infusion-related reaction, pain, tachycardia, vomiting, cough, nausea, diarrhea, decreased appetite, hypertension, fatigue, erythema multiforme,, peripheral neuropathy, urticaria, pyrexia, headache, injection site reaction, edema, anxiety, localized edema and irritability. The most common Grade 3 or 4 laboratory abnormalities (≥5% in either study) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased platelet count, decreased potassium, increased alanine aminotransferase, decreased glucose, decreased calcium, decreased albumin, decreased sodium and decreased phosphate.

{DANYELZA, naxitamab-gqgk}

The safety profile of naxitamab demonstrated the potential for severe infusion-related reactions and neurotoxicity, and the review team felt that a black box warning was indicated to advise providers of these risks. However, the review team considers that naxitamab may be safely delivered to patients with appropriate guidance in the product label, oversight from trained pediatric oncology providers who are experienced in managing similar toxicities, and administration in infusion centers equipped to respond rapidly to infusion-related reactions. The clinical reviewers do not recommend a REMS be implemented for naxitamab given these considerations. Risk management based on labeling, including a black box warning, and routine pharmacovigilance will be employed to ensure the safe and effective use of naxitamab.

The safety population included patients 1 to 24 years of age across both studies, with a median age of 5 years in both studies. Although relatively few young adult patients and very young patients (2 years of age or younger) were enrolled, exploratory analyses of safety trends did not demonstrate a significant difference in safety across groups.

In summary, the benefit: risk assessment is favorable for the use of naxitamab for the treatment of patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a response of partial response, minor response or stable disease to prior therapy. Naxitamab has demonstrated significant and clinically meaningful evidence of anti-tumor activity including confirmed ORR and evidence of durability of responses in previously treated patients with high risk neuroblastoma in the bone or bone marrow. The safety profile of naxitamab is acceptable given the serious and life-threatening nature of relapsed and refractory high-risk neuroblastoma in the bone or bone marrow, evidence of substantial anti-tumor activity, and the lack of approved therapies in this population.

The reviewers recommend accelerated approval under Subpart E (21 CFR 601.41) for naxitamab, in combination with GM-CSF, for the treatment of patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a response of stable disease, partial response or minor response to prior therapy. Accelerated approval is recommended given the small sample size and need for additional multicenter data to confirm the efficacy and safety of naxitamab. Clinical benefit will be verified and further characterized by submission of data on response rate and durability of response from additional patients who will enroll across multiple sites in the ongoing clinical trial, Study 201.

{DANYELZA, naxitamab-gqgk}

X

X

Primary Statistical Reviewer
Xiaoxue Li

Statistical Team Leader
Pallavi Mishra-Kalyani

X

X

Primary Clinical Reviewer
Diana Bradford

Clinical Team Leader
Amy Barone

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not refer this BLA to the Oncologic Drug Advisory Committee (ODAC) because, in the setting of the boxed warning and other advice in the product labeling, the safety profile is acceptable for the treatment of the indicated population and the application did not raise significant public health questions regarding the role of naxitamab for this indication. Outside expertise was not necessary as there were no controversial issues that could benefit from an ODAC discussion.

10 Pediatrics

The Applicant's Position:

Neuroblastoma nearly exclusively affects young children: 60% of cases occur before 2 years of age, and 97% occur by 10 years of age.[2] Naxitamab for the treatment of neuroblastoma was granted a Rare Pediatric Disease Designation by FDA. In addition, naxitamab for the treatment of neuroblastoma has orphan drug status; therefore, naxitamab is exempt from the requirements of PREA.

The FDA's Assessment:

FDA agrees that naxitamab is exempt from the requirements of PREA. Please see described demographics for the safety and efficacy populations in Sections 8.1 and 8.2.

11 Labeling Recommendations

The Applicant's Position:

Y-mAbs submitted draft labeling with the BLA. The draft labeling included physician labeling and carton and container labels.

The FDA's Assessment of the Prescribing Information:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Boxed Warning		A boxed warning that describes a concise summary of the adverse reactions and associated risk mitigation strategies for serious infusion-related reactions (based on subsection 5.1) and neurotoxicity (based on subsection 5.2) was added to the labeling by FDA. Consistent with the FDA Guidance: <i>Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products</i> guidance, these serious adverse reactions were described in a boxed warning because they can be prevented, reduced in frequency, or severity by appropriate use of the product.
INDICATIONS AND USAGE	Indication originally proposed for patients with high risk, relapsed or refractory neuroblastoma of the bone or bone marrow	Revised indication to note that DANYELZA is indicated in combination with granulocyte-macrophage colony-stimulating

Version date: July 24, 2019 (ALL NDA/BLA reviews)

Reference ID: 4707829

{DANYELZA, naxitamab-gqgk}

	(b) (4)	Dosage Modification) and also revised to: • Include a consolidated management strategy for all infusion-related reactions and remove (b) (4) • Include discontinuation of DANYELZA for all patients who developed anaphylaxis given the severity of this condition. • Include dosage modification recommendations for pain, peripheral neuropathy, neurological disorders of the eye, and prolonged urinary retention.
WARNINGS AND PRECAUTIONS	• Warnings initially read (b) (4)	The WARNINGS AND PRECAUTION subsections were revised to include a succinct description of each adverse reaction (e.g., incidence and severity based on CTCAE Grade observed in the clinical trials) consistent with the FDA Guidance: <i>Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products</i>. The warning and precaution with an applicant proposed title of, (b) (4), was revised to <i>Serious Infusion-Related Reactions</i>. The signs and symptoms associated with

{DANYELZA, naxitamab-gqgk}

		infusion reactions (b) (4) [REDACTED] were consolidated into a description of infusion-related reactions. A warning and precaution entitled <i>Neurotoxicity</i> was added, which included subsections for (b) (4) [REDACTED] pain, transverse myelitis and PRES. Subheadings of peripheral neuropathy, neurological disorders of the eye, and prolonged urinary retention were also added to this warning and precaution.
ADVERSE REACTIONS		Revisions to this section were made in accordance with the FDA Guidance: <i>Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format</i> and in a format consistent with recently approved oncology labeling. The statement of most common adverse reactions for Trials 201 and 12-230 was combined to provide a more informative summary of common adverse reactions. Tables for adverse reactions were revised to include appropriate

{DANYELZA, naxitamab-gqgk}

		pooled terms. Data concerning dose interruptions and permanent discontinuation of DANYELZA due to adverse reactions were included. The Postmarketing Experience/Spontaneous Reports subsection was added to describe an adverse reaction observed with expanded access.
(b) (4)		
USE IN SPECIFIC POPULATIONS	8.1 Pregnancy 8.2 Lactation	8.1: Revised based on 21CFR 201.57(c)(9)(i) to include the lack of human and animal data and required background risk statement and in a format that is consistent with recently approved oncology labeling. 8.2: Revised in accordance with the format used in recently approved oncology labeling and to include the duration of time to refrain from breastfeeding after treatment with DANYELZA. 8.3 Added the "Pregnancy Testing" heading

{DANYELZA, naxitamab-gqgk}

		consistent with 21CFR201.57(c)(9)(iii) 8.4 Revised to include a description of the pediatric population for which safety and effectiveness have been established and have not been established, consistent with 21CFR201.57(c)(9)(iv) 8.5: Revised the <i>Geriatric Use</i> subsection stating that neuroblastoma is largely a disease of pediatric and young adult patients and that the clinical studies with DANYZELA did not include patients 65 years of age and older.  (b) (4) were removed because there were so clinically significant data/recommendations to discuss.
DESCRIPTION		Revised to include the established pharmacologic class consistent with 21CFR201.57(c)(12).
CLINICAL PHARMACOLOGY		12.1 <i>Mechanism of Action</i> : Revised to describe the mechanism of action for the approved indication.

{DANYELZA, naxitamab-gqgk}

		12.2 Pharmacodynamics: Removed the proposed text and instead included a statement stating that the exposure response relationship and time course of pharmacodynamic response for safety and effectiveness have not been fully characterized. 12.3 Pharmacokinetics: FDA requested that the C_{max} geometric mean be derived from data from Trial 201, (b) (4). Revised to include information regarding the lack of effect of age, sex and race on clearance of naxitamab-gqgk.
CLINICAL STUDIES	Described Trial 12-230 and Trial 201	Revised to describe Trial 201 prior to Trial 12-230. Revised description of clinical studies to reflect the population of patients with relapsed or refractory high-risk neuroblastoma in bone or bone marrow and demonstrated a response of stable disease or better following initial or subsequent therapy. Revised description of clinical studies for clarity, brevity, and to remove (b) (4).

{DANYELZA, naxitamab-gqgk}

		(b) (4) in accordance with best labeling practices.
PATIENT COUNSELING INFORMATION		Revised to reflect the risk information that was revised in the WARNINGS AND PRECAUTIONS section and Lactation subsection.

{DANYELZA, naxitamab-gqgk}

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

In the opinion of the review team, a REMS was not necessary for the proposed application. A black box warning was included in the product label to advise healthcare providers of the risks of infusion-related reactions and neurotoxicity.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following postmarketing requirements and commitments were requested by FDA and agreed upon by the Applicant. Please also refer to the approval letter for the agreed-upon timeline for submission of PMR/PMCs and for CMC PMRs.

Nonclinical PMR/PMC

PMR# 3950-3

Rationale for PMR:

There are outstanding questions related to the toxicity of naxitamab, particularly regarding neuropathic pain and nerve damage associated with the use of the antibody and reversibility of such outcomes in the indicated patient population. Due to the lack of changes in nociception in the nonclinical toxicology studies provided in the BLA and the age of the animals used, an additional toxicology study in juvenile animals of a relevant species is needed to adequately characterize the risk of the use of naxitamab on the central and peripheral nerves as related to the indicated pediatric population.

PMR Description:

Conduct a repeat-dose juvenile animal toxicology study (a minimum of 2 cycles) in a pharmacologically relevant species that is also relevant for the toxicological analysis of an antibody with immune-mediated effects that will measure the toxicity associated with the use of naxitamab, particularly effects on the central and peripheral nervous system. Administration of naxitamab should be reflective of the clinical administration schedule. Incorporate an evaluation of the effect of treatment on the proximal and distal nerves, and evaluation of the C1 level of the spinal cord in this study and include 7-8 slices for histopathological assessment of the brain. Evaluate the potential for effects on nociception and pain threshold, both acute and long-term, both during the study and at the end of an appropriate recovery period.

{DANYELZA, naxitamab-gqgk}

Clinical Pharmacology PMR/PMC

PMC# 3950-4

Rationale for PMC:

The BLA for naxitamab included five clinical studies (12-230, 11-009, 12-116, 2PRO1, and 201), with trials 12-230, 11-009, and 12-116 conducted by MSKCC, with study 12-230 considered to be the pivotal trial for both the safety and efficacy of Naxitamab. Study 2PRO1 and Trial 201 are currently being conducted by the Applicant and are evaluating the efficacy and safety of naxitamab in the indicated patient population. The immunogenicity of naxitamab has not been adequately characterized as only 25 out of the estimated 85 patients have been enrolled and had data available for review in the currently ongoing Applicant conducted Trial 201. The current data from Study 201 provides reliable pharmacokinetics (PK) and anti-product antibody (ADA) testing results with fully validated PK and ADA assays in a very limited number of patients (n=4). The PK and ADA results from the three trials conducted by MSKCC are deemed not reliable because the PK and ADA assays used in these trials are not fully validated. An immunogenicity testing plan should be incorporated in this trial and any future planned trials to adequately characterize the incidence of ADA and their impact on PK, efficacy and safety of naxitamab and provide reliable information to the product labeling.

PMC Description:

Conduct immunogenicity testing in all patients enrolled in the ongoing multicenter clinical trial (Trial 201) of naxitamab using the validated assays to adequately characterize the incidence of anti-drug antibody (ADA) and neutralizing antibodies against naxitamab and assess the impact of ADA on the pharmacokinetics (PK), safety and efficacy of naxitamab in accordance with FDA Guidance for Industry: [Immunogenicity Assessment for Therapeutic Protein Products](https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf) available at <https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf>. Submit the integrated immunogenicity assessment report in the final report submission. The results from this study may inform product labeling.

Clinical PMRs

PMR #3950-1

Rationale for PMR:

Naxitamab is being considered under accelerated approval for the treatment of patients with relapsed or refractory neuroblastoma in bone or bone marrow who have

{DANYELZA, naxitamab-gqgk}

demonstrated a response of stable disease or better following initial or subsequent therapy. Approval is based upon the results of a single center study and an interim analysis for an ongoing multicenter study. Continued approval may be contingent upon verification and description of clinical benefit through submission of additional efficacy data from additional patients in the ongoing multicenter clinical trial (Study 201).

PMR Description:

Submit the final report, including datasets, from an ongoing multicenter clinical trial to verify and further characterize the clinical benefit of naxitamab for the treatment of patients with relapsed or refractory neuroblastoma in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) in bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy; and to provide a more precise estimation of overall response rate and duration of response (according to the revised International Neuroblastoma Response Criteria by blinded independent review). Enroll a minimum of 80 patients with evaluable disease and systematically follow all responding patients for at least 12 months from the onset of response, or until disease progression, whichever comes first. Include subgroup analyses of overall response rate and duration of response by prior anti-GD2 exposure, disease status (refractory vs. relapsed disease), anti-drug antibody (ADA) status (neutralizing antibody [nAb] positive versus nAb negative, ADA positive versus ADA negative), and area of disease involvement (bone marrow vs. bone) in the final report reflecting a sufficient number of patients in relevant subgroups. Derive the clinical data from a minimum of six study sites, with at least five patients enrolled per site in at least five sites.

PMR# 3950-2

Rationale for PMR:

Serious infusion reactions have occurred with naxitamab, necessitating a boxed warning. The product labeling included the following terms, occurring the day of or the day following infusion, to capture serious infusion reactions: hypotension, bronchospasm, flushing, wheezing, stridor, urticaria, dyspnea, pyrexia, infusion related reaction, face edema, swelling face, (b) (4), periorbital edema, lip edema, lip swelling, tongue edema, swollen tongue, mouth swelling, (b) (4), respiratory tract edema, chills, hypoxia, pruritis, erythema multiforme, and (b) (4). The majority of the safety data is derived from a single center, where the product was developed and management of these serious reactions at this center may not be representative of experience at additional centers. Post-marketing data will not be

{DANYELZA, naxitamab-gqgk}

sufficient to characterize the risk given the level of detail available regarding management of infusion reactions such as premedication, rescue medications, infusion interruptions and discontinuation of naxitamab. Due to the limited, single-arm nature of the safety database of naxitamab at the time of this accelerated approval, additional clinical data from the ongoing multicenter study is needed to adequately characterize the risk in a broader, multicenter experience.

PMR Description:

Conduct a comprehensive analysis evaluating and characterizing the incidence, clinical presentation, management, and outcome of the potential serious risk of naxitamab-associated infusion-related reactions in a sufficient number of patients to adequately characterize the risk. Submit an integrated final report containing data using the preferred terms included in product labelling from patient-level and pooled analyses of on-going and completed clinical trials, post-marketing reports and/or literature reports and a comprehensive pharmacovigilance assessment for this potential serious risk. The report should also include an analysis of pre-medication administered. The results from this report may inform product labelling.

{DANYELZA, naxitamab-gqgk}

14 Division Director (DHOT) (NME ONLY)

X

John Leighton

{DANYELZA, naxitamab-gqgk}

15 Division Director (OCP)

X

Nam Atiqur Rahman

{DANYELZA, naxitamab-gqgk}

16 Division Director (OB)

X

Shenghui Tang

{DANYELZA, naxitamab-gqgk}

17 Acting Deputy Division Director (Clinical)

I have reviewed and concur with the review teams' analyses and recommendation to grant accelerated approval to naxitamab in combination with GM-CSF for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

X

Martha Donoghue, MD

{DANYELZA, naxitamab-gqgk}

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

Marc Theoret, MD

19 Appendices

19.1. References

The Applicant's References:

1. American Cancer Society website. *Key Statistics About Neuroblastoma*. Accessed May 14, 2020]; Available from: <https://www.cancer.org/cancer/neuroblastoma/about/key-statistics.html>.
2. Matthay, K.K., *Neuroblastoma: biology and therapy*. Oncology (Williston Park), 1997. **11**(12): p. 1857-66; discussion 1869-72, 1875.
3. Cole, K.A. and J.M. Maris, *New strategies in refractory and recurrent neuroblastoma: translational opportunities to impact patient outcome*. Clin Cancer Res, 2012. **18**(9): p. 2423-2428.
4. Maris, J.M., et al., *Neuroblastoma*. Lancet, 2007. **369**(9579): p. 2106-2120.
5. Cotterill, S.J., et al., *Clinical prognostic factors in 1277 patients with neuroblastoma: results of The European Neuroblastoma Study Group 'Survey' 1982-1992*. Eur J Cancer, 2000. **36**(7): p. 901-908.
6. Pinto, N.R., et al., *Advances in Risk Classification and Treatment Strategies for Neuroblastoma*. J Clin Oncol, 2015. **33**(27): p. 3008-3017.
7. Basta, N.O., et al., *Factors associated with recurrence and survival length following relapse in patients with neuroblastoma*. Br J Cancer, 2016. **115**(9): p. 1048-1057.
8. Kreissman, S.G., et al., *Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma (COG A3973): a randomised phase 3 trial*. Lancet Oncol, 2013. **14**(10): p. 999-1008.
9. Modak, S. and N.K. Cheung, *Neuroblastoma: Therapeutic strategies for a clinical enigma*. Cancer Treat Rev, 2010. **36**(4): p. 307-317.
10. Morgenstern, D.A., et al., *Prognostic significance of pattern and burden of metastatic disease in patients with stage 4 neuroblastoma: A study from the International Neuroblastoma Risk Group database*. Eur J Cancer, 2016. **65**: p. 1-10.
11. London, W.B., et al., *Clinical and biologic features predictive of survival after relapse of neuroblastoma: a report from the International Neuroblastoma Risk Group project*. J Clin Oncol, 2011. **29**(24): p. 3286-3292.
12. Garaventa, A., et al., *Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry*. Eur J Cancer, 2009. **45**(16): p. 2835-2842.

{DANYELZA, naxitamab-gqgk}

13. London, W.B., et al., *Historical time to disease progression and progression-free survival in patients with recurrent/refractory neuroblastoma treated in the modern era on Children's Oncology Group early-phase trials*. Cancer, 2017. **123**(24): p. 4914-4923.
14. Cheung, N.K., et al., *Humanizing murine IgG3 anti-GD2 antibody m3F8 substantially improves antibody-dependent cell-mediated cytotoxicity while retaining targeting in vivo*. Oncoimmunology, 2012. **1**(4): p. 477-486.
15. Park, J.R., et al., *Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting*. J Clin Oncol, 2017. **35**(22): p. 2580-2587.
16. Cohn, S.L., et al., *The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report*. J Clin Oncol, 2009. **27**(2): p. 289-297.

The FDA's References:

American Cancer Society website. *Key Statistics About Neuroblastoma*. Accessed May 14, 2020]; Available from: <https://www.cancer.org/cancer/neuroblastoma/about/key-statistics.html>.

Cole, K.A. and J.M. Maris, *New strategies in refractory and recurrent neuroblastoma: translational opportunities to impact patient outcome*. Clin Cancer Res, 2012. **18**(9): p. 2423-2428.

Cotterill, S.J., et al., *Clinical prognostic factors in 1277 patients with neuroblastoma: results of The European Neuroblastoma Study Group 'Survey' 1982-1992*. Eur J Cancer, 2000. **36**(7): p. 901-908.

Kushner BH, Cheung NK. GM-CSF enhances 3F8 monoclonal antibody-dependent cellular cytotoxicity against human melanoma and neuroblastoma. Blood. 1989; 73(7): 1936 – 1941.

LaCasce AS, Castells MC, Burstein HJ, Meyerhardt JA. "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy." UpToDate, updated April 28, 2020. Accessed May 15, 2020.

Maris, J.M., et al., *Neuroblastoma*. Lancet, 2007. **369**(9579): p. 2106-2120.

Matthay, K.K., *Neuroblastoma: biology and therapy*. Oncology (Williston Park), 1997. **11**(12): p. 1857-66; discussion 1869-72, 1875.

{DANYELZA, naxitamab-gqgk}

PDQ® Pediatric Treatment Editorial Board. PDQ Neuroblastoma Treatment. Bethesda, MD: National Cancer Institute. Updated June 8, 2020. Available at: <https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq>. Accessed July 29, 2020. [PMID: 26389190]

19.2. Financial Disclosure

The Applicant's Position:

Y-mAbs included financial disclosure information for clinical investigators from Trials 11-009, 12-116, 12-230, and 201, along with retrospective Study 2PR01, in the BLA. Trials 11-009, 12-116, and 12-230 were sponsored by Memorial Sloan Kettering Cancer Center (MSK) and were conducted under IND 112594. Trial 201 and retrospective Study 2PR01 were sponsored by Y-mAbs.

Y-mAbs provided a description of the steps taken to minimize bias of clinical trial results by any of the disclosed arrangements or interests.

Table 19-1 Summary of Disclosable Financial Arrangements and Interest

(b) (6)



The FDA's Assessment:

Additional information regarding the disclosures is provided below. Note that the sponsor has provided tables for Trials 12-116, 2PR01, and 11-009, which FDA does not consider to be primary studies supporting the efficacy or safety of naxitamab, in addition to information for Trials 201 and 12-230.

(b) (6)



{DANYELZA, naxitamab-gqgk}

(b) (6)

Table 19-2: FDA Analysis of Disclosable Financial Interests

(b) (6)

{DANYELZA, naxitamab-gqgk}

Covered Clinical Study (Name and/or Number):* Trial 12-230

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>10</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>2</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>1</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>1</u> Significant equity interest held by investigator in study: <u>1</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from 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:	Yes ☐	No ☒ (Request explanation from Applicant)

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

{DANYELZA, naxitamab-gqgk}

Covered Clinical Study (Name and/or Number):* Trial 201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>24</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</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>1</u> Significant payments of other sorts: <u>0</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 ☒	No ☐ (Request details from 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:	Yes ☐	No ☒ (Request explanation from Applicant)

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

{DANYELZA, naxitamab-gqgk}

Covered Clinical Study (Name and/or Number):* Study 2PR01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>6</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)): 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>0</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 ☐	No ☒ (Request details from 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:	Yes ☐	No ☒ (Request explanation from Applicant)

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

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

{DANYELZA, naxitamab-gqgk}

Covered Clinical Study (Name and/or Number):* Trial 12-116

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>11</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</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>1</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>1</u> Significant equity interest held by investigator in study: <u>1</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from 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:	Yes ☐	No ☒ (Request explanation from Applicant)

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

{DANYELZA, naxitamab-gqgk}

Covered Clinical Study (Name and/or Number):* Trial 11-009

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>16</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</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>2</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>1</u> Significant equity interest held by investigator in study: <u>1</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from 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:	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

The Applicant's Position:

All relevant nonclinical data from the naxitamab program is summarized in Section 5.

The FDA's Assessment:

See Section 5.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Population PK Analysis

The Applicant conducted a population PK analysis to characterize the PK of naxitamab, identify covariate factors that could affect naxitamab disposition and compare the individual exposure estimates for subsequent exposure-response analyses. Data were collected across the trials 11-009, 12-116 and 12-230 conducted at the Memorial Sloan Kettering Cancer Center (MSKCC) and Trial 201 conducted by the Applicant. The studies included in the population PK analysis and the PK sampling times are shown in Table 19-3.

{DANYELZA, naxitamab-gqgk}

Table 19-3. Overview of studies included in the population PK analysis.

Trial ID	Trial Title	Dose Level (per dose)	N Subjects with PK Data	PK Sampling
11-009	Phase I trial of Humanized 3F8 Monoclonal Antibody (hu3F8) in subjects with High-Risk Neuroblastoma and GD2-Positive Tumors	0.1 to 1.5 mg/kg on day 1 and 8	23	predose and at 5 minutes and 3, 6 to 8, 24, 48, 72, 96, 120, and 168 h post-infusion
12-016	Phase I trial of Humanized 3F8 Monoclonal Antibody (hu3F8) when combined with IL-2 in subjects with High-Risk Neuroblastoma and GD2-Positive Solid Tumors	0.3 to 1.2 mg/kg on day 1 and 8	12	predose and at 5 minutes and 3, 6 to 8, 24, 48, 72, 96, 120, and 168 h post-infusion
12-230	Phase I/II trial of Combination Therapy of Antibody hu3F8 with GM-CSF in subjects with Relapsed/Refractory High-Risk Neuroblastoma	0.3 to 3.2 mg/kg per dose on day 1, 3 and 5	55	predose and at 5 minutes and 3, 6 to 8, 24, 48, 72, 96, 120, 168, 216 and 264 h post-infusion
201	Pivotal Phase II Trial of Naxitamab (hu3F8) and GMCSF in High-Risk Neuroblastoma Patients with Primary Refractory Disease or Incomplete Response to Salvage Treatment in Bone and/or Bone Marrow	3 mg/kg per infusion on D1, D3 and D5 of each cycle	23	Cycle 1: predose, 15 min (during infusion D1&D3), EOI and at 10 min, 1, 3, 6, 24, 168, 264, 384 and 552 h post-infusion. From cycle 2 onwards: predose (D1)

N: Number of. In several subjects, PK samples were also obtained at 1 and 2 hours post-infusion on day 1 and 8 in trial 11-009

Source: *The Applicant's population PK report (hu3F8-MS-02), Page 23, Table 1.*

The majority of patients in the primary patient population were white (74.3%) and 14.2% were Asian. The median age of all patients was 7 years old (range: 1 - 34), 65.5% were males and the median body weight (BW), body surface area (BSA), lean body mass (LBM) and body mass index (BMI) were 22.2 kg (range: 11.5 - 90 kg), 0.87 m² (range: 0.5 – 2.12), 15.8 kg/m² (range: 12.4 – 30.8) and 15.8 kg/m² (range: 12.4 – 30.8), respectively. The majority (n=82, 72.6%) of the 113 patients were of normal liver function, 30 patients (26.5%) with mild hepatic impairment, and 1 (0.9%) with moderate hepatic impairment based on NCI hepatic impairment classification. The majority of the 113 patients had normal (n=99, 87.6%) or mildly impaired (n=13, 11.5%) renal function, and 1 (0.9%) had moderate renal impairment. No patients with severe renal

{DANYELZA, naxitamab-gqgk}

impairment or severe hepatic impairment were enrolled in these clinical trials. Demographic data and laboratory values for patients in each of the three trials are shown in Table 19-4.

Table 19-4. Summary of Demographics

Trial		201	11-009	12-116	12-230	All
		(N=23)	(N=23)	(N=12)	(N=55)	(N=113)
Gender	Female	8 (34.8%)	8 (34.8%)	3 (25.0%)	20 (36.4%)	39 (34.5%)
	Male	15 (65.2%)	15 (65.2%)	9 (75.0%)	35 (63.6%)	74 (65.5%)
Age (yr)	Mean (SD)	5.57 (2.1)	10 (5.4)	16.7 (7)	7.58 (4.9)	8.64 (5.7)
	Median (range)	5 (1 - 10)	9 (3 - 21)	15 (7 - 34)	6 (2 - 31)	7 (1 - 34)
Weight (kg)	Mean (SD)	20.8 (8)	35 (21)	59.6 (20)	24.4 (13)	29.6 (19)
	Median (range)	17.8 (11.5 - 42.2)	26.1 (15.7 - 86.5)	63.9 (23.4 - 90)	20.6 (12.2 - 87)	22.2 (11.5 - 90)
Race	White	11 (47.8%)	18 (78.3%)	10 (83.3%)	45 (81.8%)	84 (74.3%)
	Black or Afr American	1 (4.3%)	3 (13.0%)	1 (8.3%)	4 (7.3%)	9 (8.0%)
	Asian	11 (47.8%)	1 (4.3%)	0 (0.0%)	4 (7.3%)	16 (14.2%)
	Other	0 (0.0%)	1 (4.3%)	1 (8.3%)	2 (3.6%)	4 (3.5%)
Body surface area (m²)	Mean (SD)	0.81 (0.2)	1.14 (0.4)	1.63 (0.4)	0.895 (0.29)	1.01 (0.39)
	Median (range)	0.74 (0.5 - 1.34)	1 (0.68 - 2.06)	1.74 (0.85 - 2.12)	0.83 (0.53 - 2)	0.87 (0.5 - 2.12)
Body mass index (kg/m²)	Mean (SD)	15.3 (2.1)	18.1 (4.4)	21.6 (3.3)	16 (2.8)	16.9 (3.6)
	Median (range)	14.5 (12.7 - 21.8)	16.3 (14.2 - 30.6)	21.5 (17.8 - 26.9)	15.4 (12.4 - 30.8)	15.8 (12.4 - 30.8)
Lean body mass (kg)	Mean (SD)	18.2 (6.3)	29.4 (14)	47.5 (15)	20.8 (8.9)	24.9 (14)
	Median (range)	16 (10.1 - 36.7)	23.8 (13.8 - 65.3)	52.3 (20.4 - 68)	17.8 (10.9 - 53.4)	20.4 (10.1 - 68)
Height (cm)	Mean (SD)	115 (15)	135 (23)	163 (23)	120 (20)	127 (25)
	Median (range)	113 (82 - 153)	129 (102 - 179)	168 (115 - 190)	119 (86.7 - 172)	121 (82 - 190)
ALT status	Normal	18 (78.3%)	20 (87.0%)	12 (100.0%)	31 (56.4%)	81 (71.7%)
	Grade 1	3 (13.0%)	3 (13.0%)	0 (0.0%)	22 (40.0%)	28 (24.8%)
	Missing	2 (8.7%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	4 (3.5%)
AP status	Normal	20 (87.0%)	19 (82.6%)	10 (83.3%)	50 (90.9%)	99 (87.6%)
	Grade 1	1 (4.3%)	4 (17.4%)	2 (16.7%)	3 (5.5%)	10 (8.8%)
	Missing	2 (8.7%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	4 (3.5%)
eGFR status	Normal	16 (69.6%)	13 (56.5%)	9 (75.0%)	47 (85.5%)	85 (75.2%)
	Grade 1	5 (21.7%)	6 (26.1%)	3 (25.0%)	6 (10.9%)	20 (17.7%)
	Grade 2	0 (0.0%)	3 (13.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
	Missing	2 (8.7%)	1 (4.3%)	0 (0.0%)	2 (3.6%)	5 (4.4%)

The demographics of three subjects from trial 11-009 were not included in this table because baseline values for height (HT), body surface area (BSA), body mass index (BMI) and lean body mass (LBM) were not available. The median values based on the remaining subjects in trial 11-009 were imputed for this table.

{DANYELZA, naxitamab-gqgk}

Source: The Applicant's population PK report (hu3F8-MS-02), Page 27, Table 2.

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.4 using first-order conditional estimation with INTERACTION option (FOCE+I). Concentrations below the limit of quantification (BLQ) were excluded from the PK analysis. The PK samples obtained in MSKCC trials 11-009, 12-116 and 12-230 were analyzed with a partially-validated assay and the LLOQ was not defined. For Trial 201, a validated assay with a LLOQ of 70 ng/mL was used. This LLOQ of 70 ng/mL was also considered for the MSKCC trials. In total, 50 observations were reported as concentration below BLQ, which were excluded from the analysis.

A total of 1743 PK observations from 113 patients were included in the population PK analysis. The plasma concentrations of naxitamab were described by a four-compartment disposition model with linear elimination. The model included inter-individual variability (IIV) for CL and V_1 . The residual error model included proportional error terms. Covariates included sex, race, age, BW, BMI, BSA, LBM, ALT status, AP status, eGFR status, IL-2 coadministration and study effect.

The final population PK parameter estimates and bootstrap estimates for naxitamab are presented in Table 19-5. The final PK model was parameterized in terms of CL, V_1 , Q_1 , V_2 , Q_2 , V_3 , Q_3 , and V_4 . Estimated fixed and random effect parameters were estimated with good precision (%RSE < 16%). The magnitude of the interindividual variability was moderate for CL (30.2 %CV) but high for V_1 (100.8 %CV). Residual variability was moderate. The PK of naxitamab is affected by BW, IL-2 coadministration and study effect. Study effect on CL is likely a combination of different infusion times, lack of actual dosing and sampling time points in the MSKCC trials, lack of PK samples obtained during the terminal phase in the MSKCC trials, and the use of different bioanalytical assays in the MSKCC trials and Trial 201. BW was included in the final population PK model following allometric principles, where volume and clearance parameters increase less proportional to body weight (exponents are 0.577 and 0.323, respectively).

{DANYELZA, naxitamab-gqgk}

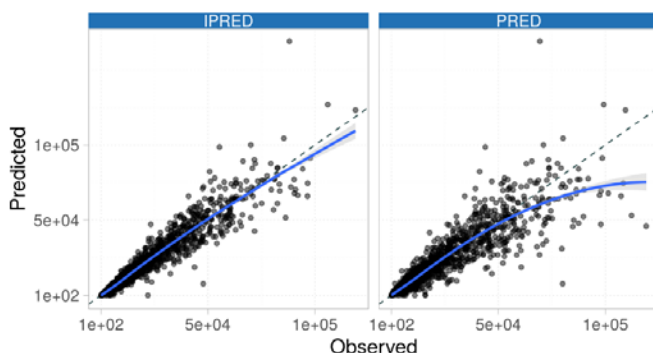
Table 19-5. Parameter estimates of the final population PK model

Parameter	Alias	Estimate	Bootstrap estimate	Relative SE %	Bootstrapped 95%CI
θ_1	CL (mL/h)	42.2	42.1		38.3 - 45.2
θ_2	V_1 (mL)	284	293		205 - 441
θ_3	Q_1 (mL/h)	14.8	14.7		10.3 - 16.3
θ_4	V_2 (mL)	$4.20 \cdot 10^3$	$4.20 \cdot 10^3$		3600 - 7050
θ_5	Q_2 (mL/h)	$3.15 \cdot 10^3$	$3.12 \cdot 10^3$		2590 - 3800
θ_6	V_3 (mL)	901	899		814 - 966
θ_7	Q_3 (mL/h)	58.0	57.2		18.9 - 77.5
θ_8	V_4 (mL)	510	513		439 - 774
θ_9	Proportional residual error	0.244	0.242	3.20	0.229 - 0.255
θ_{10}	IL-2 effect on CL (-)	0.991	0.993	12.0	0.803 - 1.2
θ_{11}	MSK study effect on CL (-)	-0.509	-0.508	7.30	-0.564 - -0.442
θ_{12}	WT effect on V	0.577	0.573	6.90	0.502 - 0.643
θ_{13}	WT effect on CL, Q	0.323	0.324	15.5	0.242 - 0.412
$\omega_{1,1}$	ω_{CL}^2	0.0913	0.0884	18.3	0.0644 - 0.12
$\omega_{2,2}$	ω_{V1}^2	1.02	0.929	37.3	0.447 - 1.64

CL: clearance; V_1 : central volume of distribution; V_2 : first peripheral volume of distribution; Q_1 : first intercompartment clearance; V_3 : second peripheral volume of distribution; Q_2 : second intercompartment clearance; V_4 : third peripheral volume of distribution; Q_3 : third intercompartment clearance; ω_X^2 : variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega_X^2} \cdot 100$; SE: standard error; CI: Confidence interval. IL-2: Interleukin-2; MSKCC: Memorial Sloan Kettering Cancer Center.

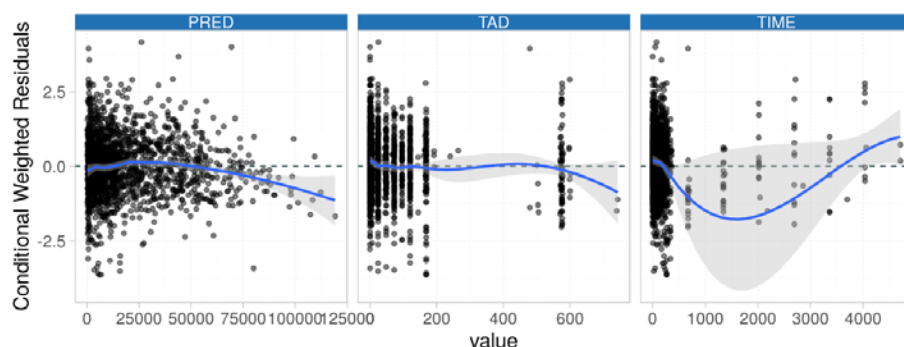
Source: The Applicant's population PK report (hu3F8-MS-02), Page 27, Table 2.

The diagnostic plots for the final PK model are shown in Figure 19-1. The VPC (visual predictive check) on the final PK model in Figure 19-2 is stratified by trial. The model described the observed data well and the model predictions were generally within the 90% prediction intervals. No apparent bias was observed in the overall model fit for the data. Bootstrap results are in good concordance with the final model parameter estimates. (Table 19-4)

Figure 19-1. Diagnostic plots for the final population PK model

Blue line and grey area: Loess smooth fit with its 95% confidence interval. Black dashed line: Line of identity; PRED: Population predicted; IPRED: Individual prediction.

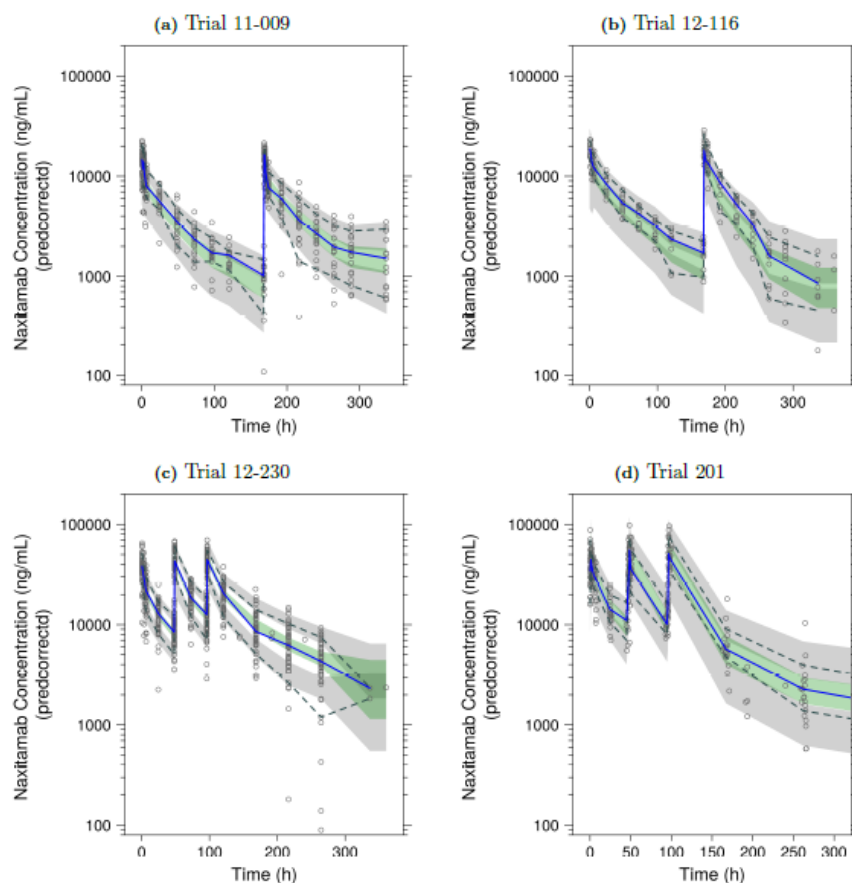
{DANYELZA, naxitamab-gqgk}



Blue line and grey area: Loess smooth fit with it's 95% confidence interval; **PRED**: Population predicted; **TAD**: Time after dose. The smoother in the CWRES versus TIME plot is hampered by the low number of samples obtained after cycle 1 resulting in a bias in the smoother. The individual CWRES values are reasonably well scattered around 0 indicating a decent fit of the model.

Source: The Applicant's population PK report (hu3F8-MS-02), Page 50, Figure 10-11.

{DANYELZA, naxitamab-gqgk}

Figure 19-2. Visual predictive check stratified by trial for final population PK model

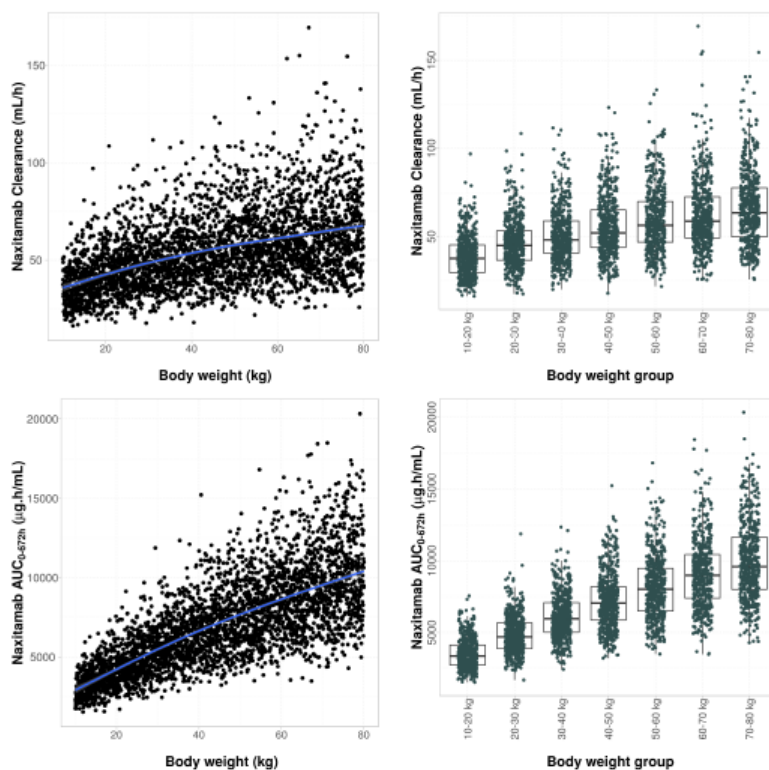
Circles: Observations, Solid Blue Line: Median of the observed naxitamab concentrations, Dashed Lines: 10th and 90th percentiles of the observed naxitamab concentrations, Shaded Area: The shaded areas indicate the 80% CI around the prediction-corrected median (green area), and 10th and 90th percentiles of the simulated concentrations (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. (Bergstrand et al., 2011).

Source: The Applicant's population PK report (hu3F8-MS-02), Page 55, Figure 17.

In the final model, the allometric BW-exponents for CL and V_1 were estimated to be 0.323 and 0.577, respectively. The effect of BW on naxitamab concentration was estimated by simulation of naxitamab concentration with different weight groups. Naxitamab exposures of AUC_{0-672h} and C_{max} are expected to increase with increasing BW as a result of the proportional increase in total administered dose and less than proportional increase in naxitamab CL (Figure 19-3, Table 19-6, Figure 19-4 and Table 19-7).

{DANYELZA, naxitamab-gqgk}

Figure 19-3. Simulated naxitamab clearance and AUC_{0-672h} versus body weight.



Circles: Simulated individual Naxitamab clearance (CL) and exposure (AUC_{0-672h}) predictions. **Left panel**, Blue solid line and shaded area: predicted mean with its 90% confidence interval. **(right panels)** Boxes: show the median and upper and lower quartiles (25% and 75%) of the data. Whiskers: extend to 1.5 times the interquartile range.

Source: The Applicant's population PK report (hu3F8-MS-02), Page 58, Figure 20.

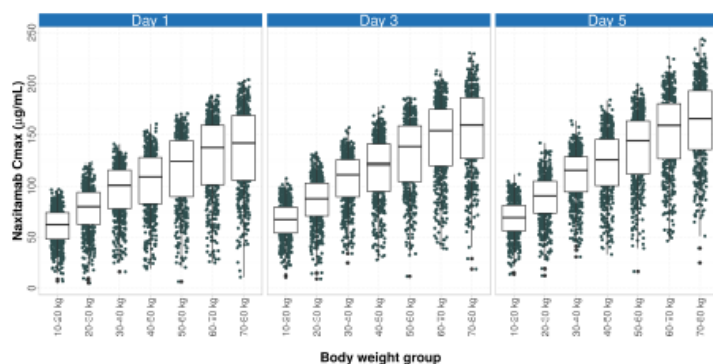
{DANYELZA, naxitamab-gqgk}

Table 19-6. Summary of simulated naxitamab clearance and AUC_{0-672h} versus bodyweight.

WT group	Total dose	n	Clearance (mL/h)		AUC_{0-672h} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	
			mean	90% CI	mean	90% CI
10-20 kg	90-180 mg	500	38.7	22.8 - 61.5	$3.52\cdot 10^3$	$2.06\cdot 10^3$ - $5.44\cdot 10^3$
20-30 kg	180-270 mg	500	46.5	27.8 - 72.0	$4.84\cdot 10^3$	$2.94\cdot 10^3$ - $7.13\cdot 10^3$
30-40 kg	270-360 mg	500	50.7	31.0 - 77.8	$6.13\cdot 10^3$	$3.70\cdot 10^3$ - $8.99\cdot 10^3$
40-50 kg	360-450 mg	500	55.5	30.7 - 88.2	$7.21\cdot 10^3$	$4.38\cdot 10^3$ - $1.11\cdot 10^4$
50-60 kg	450-540 mg	500	59.6	34.1 - 94.4	$8.14\cdot 10^3$	$4.85\cdot 10^3$ - $1.22\cdot 10^4$
60-70 kg	540-630 mg	500	62.8	36.6 - 96.7	$9.09\cdot 10^3$	$5.55\cdot 10^3$ - $1.33\cdot 10^4$
70-80 kg	630-720 mg	500	66.1	37.4 - 103	$9.96\cdot 10^3$	$6.06\cdot 10^3$ - $1.51\cdot 10^4$

Simulated Naxitamab exposure by weight group for the final PopPK model. **n**: Number of subjects; **CI**: Confidence interval.

Source: The Applicant's population PK report (hu3F8-MS-02), Page 59, Table 11.

Figure 19-4. Simulated naxitamab C_{max} on Day 1, Day 3 and Day 5 versus bodyweight group

Circles: Simulated individual Naxitamab C_{max} predictions Boxes: show the median and upper and lower quartiles (25% and 75%) of the data Whiskers: extend to 1.5 times the interquartile range.

Source: The Applicant's population PK report (hu3F8-MS-02), Page 59, Figure 21.

{DANYELZA, naxitamab-gqgk}

Table 19-7. Summary of simulated naxitamab C_{max} on Day 1, Day 3 and Day 5 versus bodyweight group

WT group	Total dose	Day	n	C _{max} (µg/mL)	
				mean	90% CI
10-20 kg	90-180 mg	Day 1	500	60.4	29.4 - 87.5
		Day 3	500	66.2	35.0 - 93.5
		Day 5	500	68.2	37.5 - 95.7
20-30 kg	180-270 mg	Day 1	500	76.6	35.0 - 108
		Day 3	500	85.0	43.4 - 118
		Day 5	500	88.1	47.0 - 122
30-40 kg	270-360 mg	Day 1	500	94.7	43.6 - 127
		Day 3	500	106	55.2 - 139
		Day 5	500	110	60.6 - 143
40-50 kg	360-450 mg	Day 1	500	103	42.6 - 145
		Day 3	500	116	55.0 - 160
		Day 5	500	121	62.0 - 165
50-60 kg	450-540 mg	Day 1	500	116	51.1 - 160
		Day 3	500	131	66.1 - 176
		Day 5	500	137	73.9 - 183
60-70 kg	540-630 mg	Day 1	500	129	58.5 - 177
		Day 3	500	145	73.9 - 195
		Day 5	500	152	81.2 - 203
70-80 kg	630-720 mg	Day 1	500	136	63.4 - 189
		Day 3	500	154	82.3 - 209
		Day 5	500	162	91.4 - 218

n: Number of subjects; CI: Confidence interval.

Source: The Applicant's population PK report (hu3F8-MS-02), Page 61, Table 12.

ADA formation was tested for 157 patients in Trials 11-009, 12-116, 12-230 (Phase 1 only) and 201 (Table 19-8). The ADA samples obtained in Trial 201 were analyzed using a multi-tiered approach consisting of screening, confirmatory and neutralizing antibody testing with validated assays, and samples were categorized as either negative or positive. The samples obtained in MSKCC trials (11-009, 12-116 and 12-230) were analyzed with a partially-validated screening assay only.

Table 19-8. Overview of number of patients with ADA formation by trial

Trial	Trial Part	Total Number of patients	Patients with ADA+ and PK		Patients with ADA+	
			N	Percentage	N	Percentage
11-009	2 infusions/cycle	23	4	17%	6	26%
	3 infusions/cycle	44	5	11%	10	23%
12-116		12	4	33%	6	50%
12-230	Phase 1	55	3	5.5%	16	29.1%
201	Interim data	23	2	8.7%	2	8.7%
Total		157	18	11.5%	40	25.5%

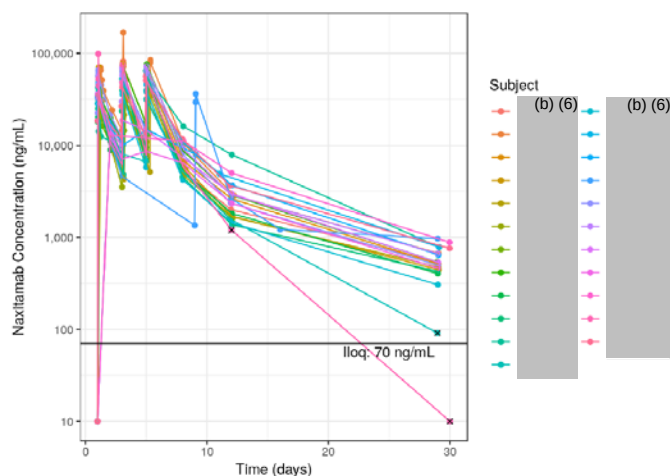
ADA: Anti-drug antibody; **Patients with ADA+ and PK:** Includes only the patients for which PK samples were obtained on the day of ADA formation (positive ADA sample) or thereafter in cycle 1; **Patients with ADA+:** Includes all patients with ADA formation (positive ADA sample) at any time during treatment irrespective of availability of PK data. Note that the interim dataset for trial 201 only included dosing, PK and ADA information for 23 patients.

Source: The Applicant's population PK report – ADA addendum (hu3F8-MS-02 addendum), Page 9, Table 1.

In total, ADA formation was observed in 40 patients (25.5%) at any time during treatment with naxitamab; however, only a small subgroup (n=18) of patients, providing both (positive) ADA data and naxitamab PK data at the day of ADA formation or thereafter during Cycle 1, was available for the evaluation of the impact of ADA formation on the naxitamab PK. The ADA effect was not evaluated in the population PK analysis.

In Trial 201, positive ADA titers were observed in 2 patients (8.7% out of 23 patients), with a total of 4 PK samples obtained at the same day or after positive ADA titers were observed. Figure 19-5 showed the individual naxitamab PK profiles. In general, reduced naxitamab concentrations during the first treatment cycle were observed in patients with ADA formation for which PK data were available at the time of ADA formation. Because PK data are not available for subsequent treatment cycles in these patients, it is uncertain whether the naxitamab exposure changes were due to ADA formation.

{DANYELZA, naxitamab-gqgk}

Figure 19-5. Naxitamab concentration in patients with and without ADA formation in Trial 201

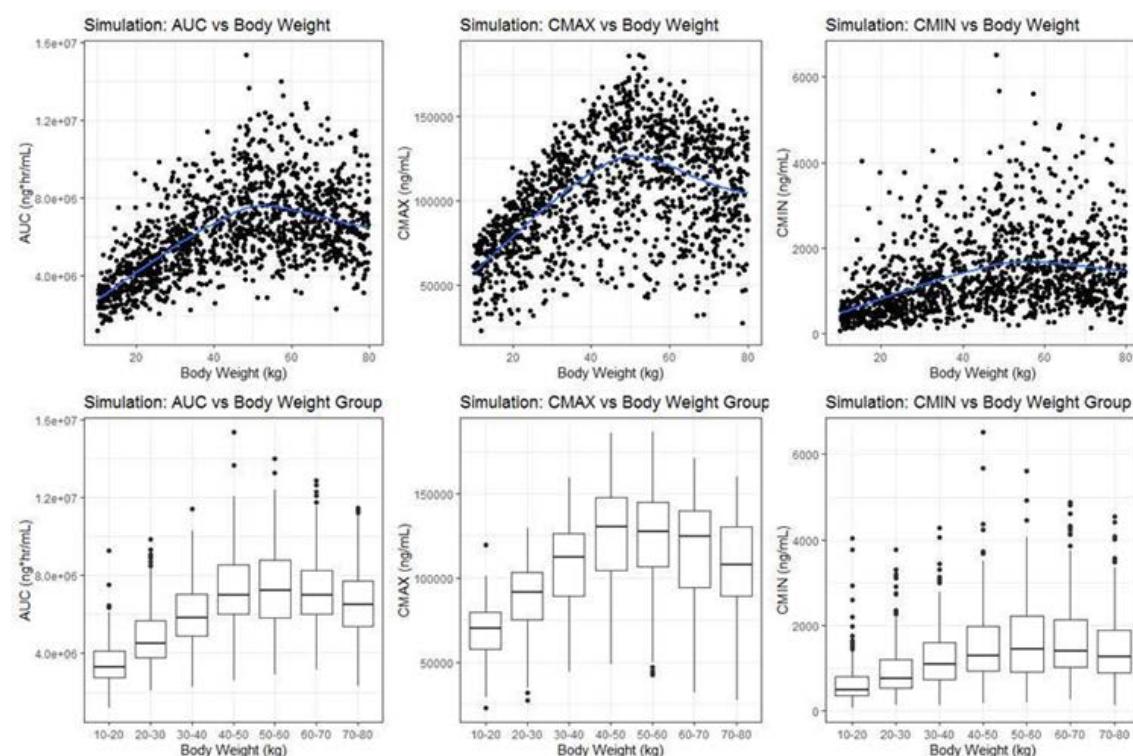
The x indicates PK samples obtained at the day of or after ADA formation was positive.

Source: The Applicant's population PK report – ADA addendum (hu3F8-MS-02 addendum), Page 35, Table 15.

Reviewer's comments:

The population PK model developed by the applicant was verified by the reviewer. The model appears to be acceptable in general because of the good agreement between observations and predictions. Based on the population PK model, naxitamab exposures are expected to increase with increasing BW (Figure 19-4). The mean predicted AUC_{0-672h} is approximately doubled in patients with BW 70-80 kg compared to the patients with BW 20-30 kg. (Table 19-6). Flat dosing in adults and older adolescents with higher BW will minimize PK variability. There were limited clinical safety experiences in patients with BW > 50 kg with doses > 450 mg per cycle (i.e., 3 patients with BW > 50 kg received dose > 450 mg/cycle with 2 patients each only received 3 infusions and 1 patient received 5 infusions) who are expected to have higher exposure compared to that observed in the clinical trials. A dosing cap of 450 mg per cycle of naxitamab for patients with BW > 50 kg was suggested by the reviewer. With the dosing cap, predicted naxitamab exposures for patients with BW higher than 50 kg are comparable to patients with lower BW (30 - 50 kg) at weight-based dosing of 3 mg/kg/day (9 mg/kg per cycle). (Figure 19-6)

{DANYELZA, naxitamab-gqgk}

Figure 19-6. Simulated naxitamab exposures versus bodyweight with dosing cap of 450 mg per cycle.*Source: Reviewer's analysis*

19.4.2 Exposure-Response for Efficacy Analysis

The exposure-response relationships of overall response rate (ORR) or complete response (CR) and naxitamab exposure were evaluated with 22 patients in trials 201 and 17 patients in Trial 12-230. Neither naxitamab exposure (AUC), nor any of the evaluated covariates were found to have a significant effect on ORR or CR. Average daily naxitamab exposure in Cycle 1 was comparable between responders and non-responders. Patients without prior anti-GD2 treatment had a slightly higher ORR or CR rate compared to those with prior anti-GD2 treatment, and ORR/CR rates were higher in Trial 201 compared to Trial 12-230. (Table 19-9)

{DANYELZA, naxitamab-gqgk}

Table 19-9. Summary of overall and complete response rates

		ORR			Complete Response		
		n	Total	Observed rate and 90% CI	n	Total	Observed rate and 90% CI
Prior anti-GD2	Yes	4	15	0.267 (0.104 - 0.512)	2	15	0.133 (0.0289 - 0.372)
	No	17	24	0.708 (0.52 - 0.849)	12	24	0.5 (0.341 - 0.659)
Baseline disease status	Primary Refractory	12	20	0.6 (0.395 - 0.778)	8	20	0.4 (0.222 - 0.605)
	Incomplete Response to Salvage Treatment	9	19	0.474 (0.278 - 0.677)	6	19	0.316 (0.153 - 0.53)
Race	White	14	24	0.583 (0.398 - 0.75)	9	24	0.375 (0.216 - 0.562)
	Black	0	2	0	0	2	0
	Asian	7	13	0.538 (0.292 - 0.769)	5	13	0.385 (0.173 - 0.642)
	Other	0	0	0	0	0	0
Trial	201	14	22	0.636 (0.44 - 0.799)	11	22	0.5 (0.335 - 0.665)
	12-230	7	17	0.412 (0.218 - 0.633)	3	17	0.176 (0.0556 - 0.401)
Age group	<6	10	19	0.526 (0.323 - 0.722)	6	19	0.316 (0.153 - 0.53)
	≥6 and <12	11	19	0.579 (0.37 - 0.765)	8	19	0.421 (0.235 - 0.63)
	≥12	0	1	0	0	1	0
Baseline MIBG score	<5	11	20	0.55 (0.35 - 0.737)	10	20	0.5 (0.327 - 0.673)
	≥5 and <10	5	11	0.455 (0.208 - 0.722)	3	11	0.273 (0.0873 - 0.564)
	≥10	5	8	0.62	1	8	0.12
AUC24 (ug,h/mL)	[45.4,123)	4	11	0.364 (0.144 - 0.646)	2	11	0.182 (0.0396 - 0.475)
	[123.0,151)	6	9	0.67	5	9	0.56
	[151.0,199)	6	10	0.6 (0.31 - 0.84)	4	10	0.4 (0.16 - 0.69)
	[199.0,490]	5	9	0.56	3	9	0.33

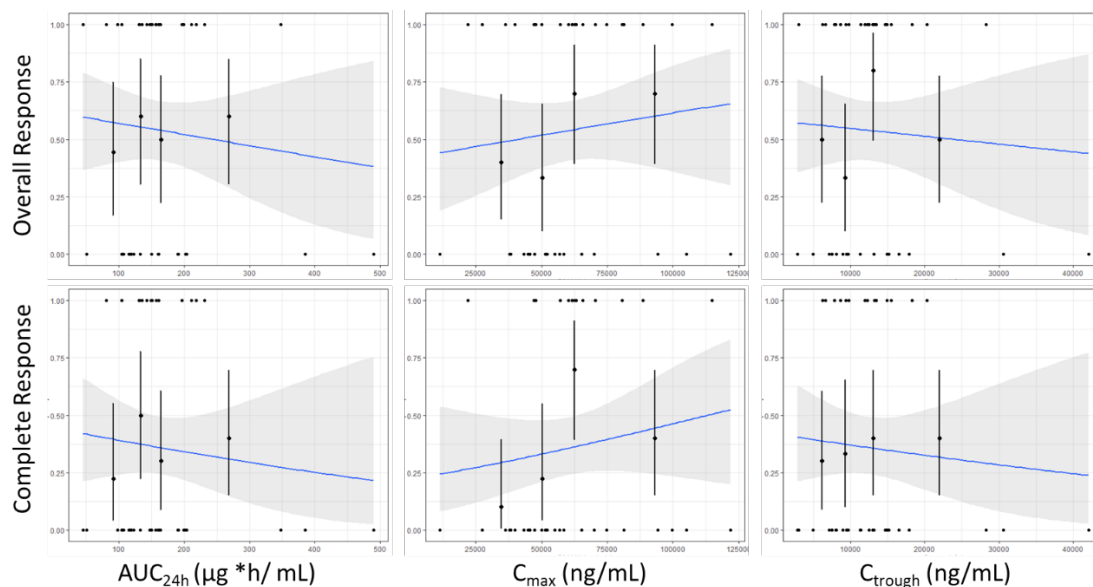
n= number of subjects with an event; Total = total number of subjects in the group

Source: The Applicant's Addendum to the Pharmacometric Analysis Report hu3F8-MS-02 (Information request response on May 29th, 2020), Page 15, Table 5.

Reviewer's comments:

The results of the exposure-efficacy analysis for naxitamab were verified by the reviewer. Logistic regression analyses identified similar shallow and non-significant relationships between exposures (AUC_{24h} , C_{max} , C_{trough}) of naxitamab and ORR. Further analysis for CR resulted in similar findings (Figure 19-7). Overall, the ER relationships between ORR/CR and exposures of naxitamab are inconclusive because of the limited data from the trials in small number of patients and potential confounding factors (e.g., ADA effect).

{DANYELZA, naxitamab-gqgk}

Figure 19-7. Logistic regression analysis of exposures of naxitamab for ORR or CR.*Source: Reviewer's Analysis*

19.4.3 Exposure-Response for Safety Analysis

The relationships between adverse event (AE) responses (Grade 2+ bronchospasm, hypertension and hypotension) and naxitamab exposures (AUC_{24h}) at steady state, age, sex, body weight, race and baseline blood pressure were evaluated in patients with advanced tumors in trials 11-009, 12-116, 12-230 and 201. The occurrence of Grade 2+ bronchospasm, hypertension and hypotension events were summarized by covariates of interest. (Table 19-10)

{DANYELZA, naxitamab-gqgk}

Table 19-10. Occurrence of grade 2+ bronchospasm, hypertension and hypotension events stratified by covariates of interest.

		Bronchospasm			Hypertension			Hypotension		
		n	Total	Observed rate and 90% CI	n	Total	Observed rate and 90% CI	n	Total	Observed rate and 90% CI
Trial	11-009	0	23	0	0	23	0	0	23	0
	12-116	1	12	0.0833 (0.00575 - 0.352)	0	12	0	2	12	0.167 (0.0362 - 0.444)
	12-230	4	55	0.0727 (0.0274 - 0.164)	3	55	0.0545 (0.0169 - 0.141)	35	55	0.636 (0.516 - 0.742)
	201	17	23	0.739 (0.547 - 0.874)	4	23	0.174 (0.0666 - 0.36)	23	23	1.00
Race	White	10	84	0.119 (0.0679 - 0.196)	6	84	0.0714 (0.0333 - 0.14)	40	84	0.476 (0.383 - 0.571)
	Black	2	9	0.22	1	9	0.11	4	9	0.44
	Asian	10	16	0.625 (0.393 - 0.816)	0	16	0	14	16	0.875 (0.647 - 0.973)
	Other	0	4	0	0	4	0	2	4	0.50
Age group	<6	11	38	0.289 (0.175 - 0.435)	2	38	0.0526 (0.0113 - 0.165)	28	38	0.737 (0.593 - 0.846)
	≥6 and <12	11	50	0.22 (0.131 - 0.34)	3	50	0.06 (0.0186 - 0.154)	25	50	0.5 (0.387 - 0.613)
	≥12	0	25	0	2	25	0.08 (0.0172 - 0.241)	7	25	0.28 (0.144 - 0.464)
AUC ₂₄ (ug.h/mL)	[5.02, 232)	0	29	0	0	29	0	4	28	0.143 (0.0545 - 0.304)
	(232.00, 448)	4	28	0.143 (0.0545 - 0.304)	0	28	0	15	30	0.5 (0.356 - 0.644)
	(448.00, 593)	7	26	0.269 (0.139 - 0.449)	3	29	0.103 (0.0322 - 0.254)	20	28	0.714 (0.542 - 0.845)
	(593.00,1910]	11	30	0.367 (0.225 - 0.533)	4	27	0.148 (0.0565 - 0.314)	21	27	0.778 (0.604 - 0.894)

n= number of subjects with an event; Total = total number of subjects in the group

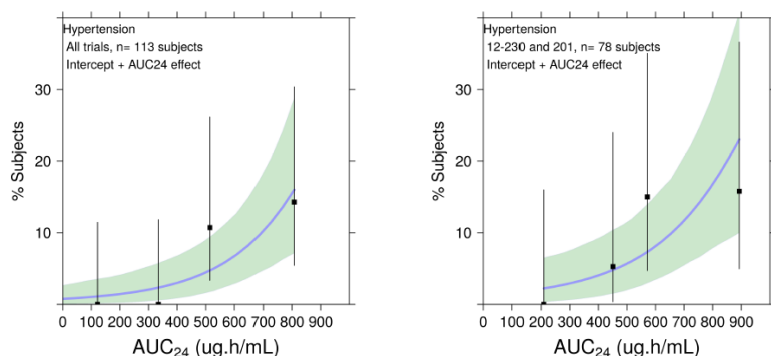
Source: *The Applicant's Addendum to the Pharmacometric Analysis Report hu3F8-MS-02 (Information request response on May 29th, 2020), Page 11, Table 1.*

As shown in Table 19-9, Asian subjects had a higher occurrence rate of Grade 2+ bronchospasm. A possible relationship between naxitamab AUC_{24h} and occurrence of bronchospasm events was observed based on a quartile analysis.

The ER analysis for hypertension identified naxitamab exposure as the only significant predictor for occurrence of Grade 2+ hypertension. Figure 19-8 showed the observed and model predicted incidence rate of hypertension events versus naxitamab AUC_{24h} quartiles. The model predictions are in line with the observed data.

{DANYELZA, naxitamab-gqgk}

Figure 19-8. Observed and predicted incidence rate of grade 2+ hypertension events versus naxitamab exposure AUC_{24h}

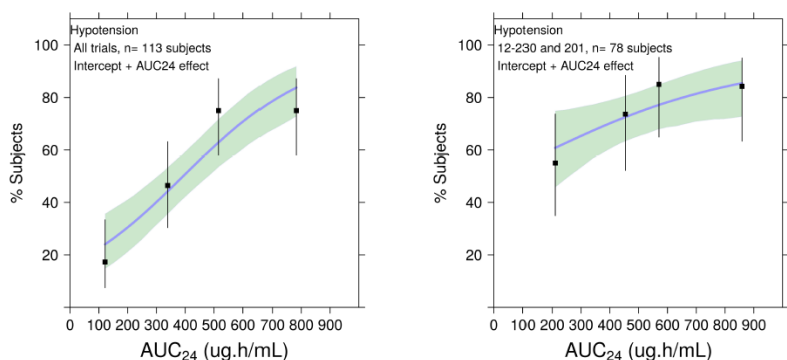


Data points depict the incidence rates of hypertension binned by exposure quartiles and plotted versus the predicted mean AUC₂₄ in each bin. Error bars depict the 90% CI of the observed incidence rate. Line and shaded area: Model predicted mean and 90% CI for the final models. Left panel: main analysis; Right panel: sensitivity analysis.

Source: The Applicant's Addendum to the Pharmacometric Analysis Report hu3F8-MS-02 (Information request response on May 29th, 2020), Page 14, Figure 3.

The ER analysis for hypotension identified a positive trend between naxitamab exposure and the occurrence of Grade 2+ hypotension. Figure 19-9 showed the observed and model predicted incidence rates of hypotension events versus naxitamab exposure. The model predictions are in line with the observed data.

{DANYELZA, naxitamab-gqgk}

Figure 19-9. Observed and predicted incidence rate of grade 2+ hypotension events versus naxitamab exposure AUC_{24h}

Data points depict the incidence rates of hypotension binned by exposure quartiles and plotted versus the predicted mean AUC₂₄ in each bin. Error bars depict the 90% CI of the observed incidence rate. Line and shaded area: Model predicted mean and 90% CI for the final models. Left panel: main analysis; Right panel: sensitivity analysis.

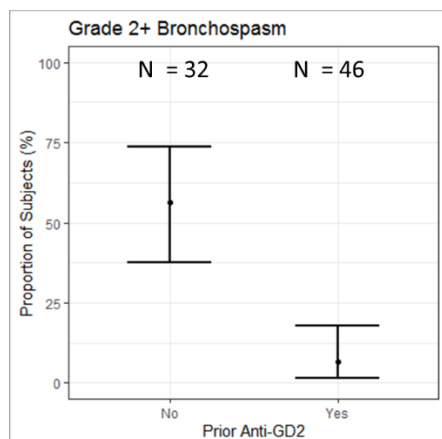
Source: The Applicant's Addendum to the Pharmacometric Analysis Report hu3F8-MS-02 (Information request response on May 29th, 2020), Page 16, Figure 4.

Reviewer's comments:

The results of the exposure-safety analysis for naxitamab were verified by the reviewer. Additional analyses were conducted for AEs (Grade 2+ bronchospasm, hypertension, hypotension and Grade 3 hypotension) by the reviewer with additional covariates of prior anti-GD2 treatment and study effect (trials 11-009, 12-116 and 12-230 conducted by MSK vs study 201 conducted by the Applicant). Study effect was included in the analysis because higher AE (Grade 2+ bronchospasm, hypertension and hypotension) rates were observed in Trial 201 compared with other trials (Table 19-9). As shown in Table 19-9, patients in MSK trials (Trial 11-009, 12-116, 12-230) had lower occurrence rates of Grade 2+ bronchospasm than patients in the Y-mAbs-sponsored trial (Trial 201). Figure 19-10 and Figure 19-11 indicate that the patients with prior anti-GD2 treatment might have lower Grade 2+ bronchospasm rate than patients without prior anti-GD2 treatment and a possible relationship between naxitamab AUC_{24h} and occurrence of bronchospasm events, but both were not identified in the analysis.

{DANYELZA, naxitamab-gqgk}

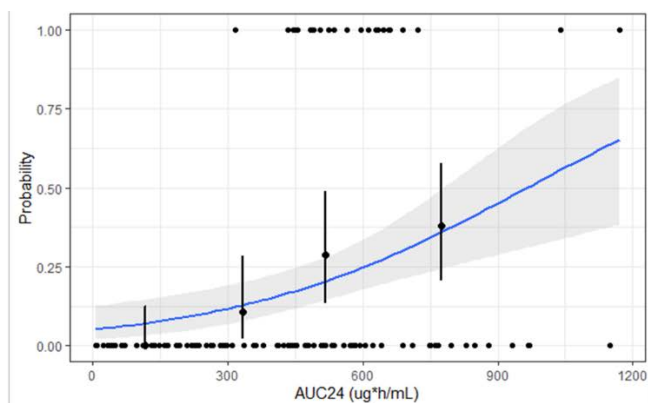
Figure 19-10. Grade 2+ bronchospasm stratified by prior Anti-GD2 treatment.



Data points depict the incidence rates of bronchospasm stratified by prior Anti-GD2 treatment. Error bars depict the 95% CI of the observed incidence rate.

Source: Reviewer's analysis.

Figure 19-11. Logistic regression of grade 2+ bronchospasm with naxitamab exposure (AUC_{24h})



Data points depict the incidence rates of bronchospasm binned by exposure quartiles and plotted versus the predicted mean AUC_{24h} in each bin. Error bars depict the 90% CI of the observed incidence rate.

Source: Reviewer's analysis.

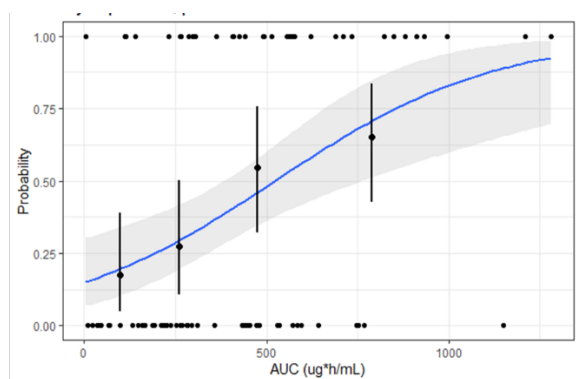
From the additional exposure-safety analysis for Grade 2+ hypertension, AUC_{24h} was identified to be the only predictor which is similar to the Applicant's result.

From the additional exposure-safety analysis for Grade 2+ hypotension, study effect and AUC_{24h} were identified to be the predictors (Figure 19-12). Slightly lower AE rate was observed in the

{DANYELZA, naxitamab-gqgk}

patients with prior Anti-GD2 treatment comparing with the patients without prior Anti-GD2 treatment (Figure 19-13). Table 19-9 and Figure 19-14 show that patients in MSK trials (Trial 11-009, 12-116, 12-230) had lower occurrence rates of Grade 3 hypotension than patients in the Y-mabs trial (Trial 201). Figure 19-15 illustrates that there is a possible relationship between naxitamab AUC_{24h} and occurrence of grade 3 hypotension, but it was not identified in the analysis.

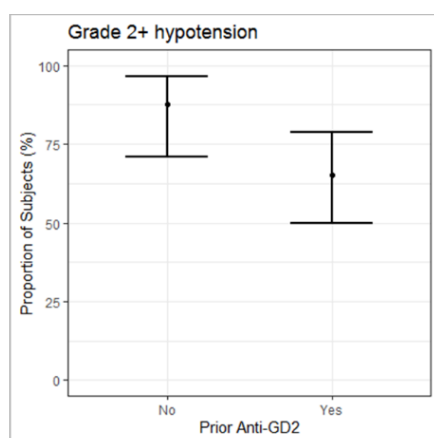
Figure 19-12. Logistic regression of Grade 2+ hypotension with naxitamab exposure (AUC_{24h}) in Study 11-009, 12-116 and 12-230



Data points depict the incidence rates of bronchospasm binned by exposure quartiles and plotted versus the predicted mean AUC_{24h} in each bin. Error bars depict the 90% CI of the observed incidence rate.

Source: Reviewer's analysis

Figure 19-13. Grade 2+ hypotension stratified by prior Anti-GD2 treatment.

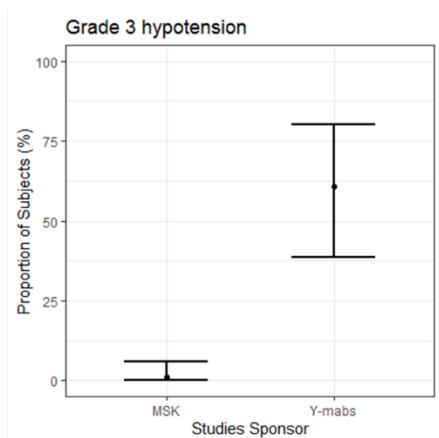


Data points depict the incidence rates of hypotension stratified by prior Anti-GD2 treatment. Error bars depict the 95% CI of the observed incidence rate.

{DANYELZA, naxitamab-gqgk}

Source: Reviewer's Analysis

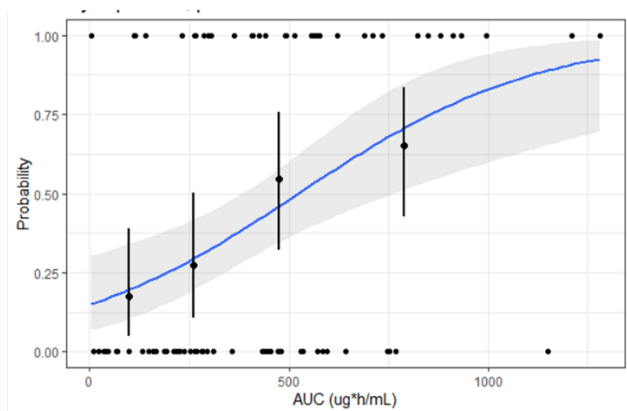
Figure 19-14. Grade 3 hypotension stratified by study



Data points depict the incidence rates of hypotension stratified by study. Error bars depict the 95% CI of the observed incidence rate.

Source: Reviewer's analysis

Figure 19-15. Logistic regression of Grade 3 hypotension with naxitamab exposure (AUC_{24h})



Data points depict the incidence rates of bronchospasm binned by exposure quartiles and plotted versus the predicted mean AUC_{24h} in each bin. Error bars depict the 90% CI of the observed incidence rate.

Source: Reviewer's analysis

{DANYELZA, naxitamab-gqgk}

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

The safety analyses performed by FDA are described in Section 8.2.

BLA 761171

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Stephanie Aungst	OOD/DHOT	Sections: 5 Nonclinical Pharmacology/Toxicology	Select one: ☒ Authored ☐ Approved
Signature: Stephanie L. Aungst - S Digitally signed by Stephanie L. Aungst -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001570045, cn=Stephanie L. Aungst -S Date: 2020.11.24 13:52:24 -05'00'				
Nonclinical Supervisor	Whitney S. Helms	OOD/DHOT	Sections: 5 Nonclinical Pharmacology/Toxicology	Select one: ☒ Authored ☒ Approved
Signature: Whitney S. Helms -S Digitally signed by Whitney S. Helms -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000585776, cn=Whitney S. Helms -S Date: 2020.11.24 14:03:58 -05'00'				
Nonclinical Team Division Director	John K. Leighton	OOD/DHOT	Sections: 5 Nonclinical Pharmacology/Toxicology	Select one: ☐ Authored ☒ Approved
Signature: John K. Leighton - S Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2020.11.24 13:54:37 -05'00'				
Clinical Pharmacology Reviewer	Catharine Bulik	OCP/DCPI	Sections: 6	Select one: ☒ Authored ☐ Approved
Signature: Catharine C. Bulik -S Digitally signed by Catharine C. Bulik -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002702169, cn=Catharine C. Bulik -S Date: 2020.11.24 13:36:31 -05'00'				
Clinical Pharmacology Team Leader	Hong Zhao	OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
Signature: Hong Zhao -S Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2020.11.24 13:59:49 -05'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman	OTS/OCP/DCPII	Sections: 6	Select one: ☐ Authored ☒ Approved
				Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2020.11.24 15:35:20 -05'00'
Pharmacometrics Reviewer	Yangbing Li	OTS/OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
				Signature: Yangbing Li -S (Affiliate) Digitally signed by Yangbing Li -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002587726, cn=Yangbing Li -S (Affiliate) Date: 2020.11.24 17:03:44 -05'00'
Pharmacometrics Team Leader	Jiang Liu	OTS/OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
				Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.11.25 10:06:02 -05'00'
Clinical Reviewer	Diana Bradford	OOD/DO2	Sections: 1, 2, 3, 4.1, 7, 8, 9, 10, 11, 12, 13	Select one: ☒ Authored ☐ Approved
				Signature: Diana L. Bradford -S Digitally signed by Diana L. Bradford -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001559418, cn=Diana L. Bradford -S Date: 2020.11.24 13:39:24 -05'00'
Clinical Team Leader	Amy Barone	OOD/DO2	Sections: 1, 2, 3, 4.1, 7, 8, 9, 10, 11, 12, 13	Select one: ☐ Authored ☒ Approved
				Signature: Amy Barone -S Digitally signed by Amy Barone -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy Barone -S, 0.9.2342.19200300.100.1.1=2001366575 Date: 2020.11.24 14:09:04 -05'00'

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Xiaoxue Li	OB/DBV	Section 8	Select one: ☒ Authored ☐ Approved
Signature: Xiaoxue Li -S Digitally signed by Xiaoxue Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaoxue Li -S, 0.9.2342.19200300.100.1.1=2002606440 Date: 2020.11.24 13:17:16 -05'00'				
Statistical Team Leader	Pallavi Mishra-Kalyani	OB/DBV	Section 8	Select one: ☒ Authored ☒ Approved
Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001675542, cn=Pallavi S. Mishra-kalyani -S Date: 2020.11.24 13:28:47 -05'00'				
Division Director (OB)	Shenghui Tang	OB/DBV	Section 8	Select one: ☐ Authored ☒ Approved
Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2020.11.24 14:05:58 -05'00'				
Associate Director for Labeling (ADL)	Ann Marie Trentacosti	OND/LPT	Section 11	Select one: ☒ Authored ☐ Approved
Signature: Ann M. Trentacosti -S Digitally signed by Ann M. Trentacosti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300216343, cn=Ann M. Trentacosti -S Date: 2020.11.24 14:17:12 -05'00'				
Cross-Disciplinary Team Leader (CDTL)	Amy Barone	OOD/DO2	Sections: 1, 2, 3, 4.1, 7, 8, 9, 10, 11, 12, 13	Select one: ☒ Authored ☒ Approved
Signature: Amy Barone -S Digitally signed by Amy Barone -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy Barone -S, 0.9.2342.19200300.100.1.1=2001366575 Date: 2020.11.24 14:10:13 -05'00'				
Deputy Division Director (Clinical)	Martha Donoghue	OOD/DO2	Sections: 1, 2, 3, 4.1, 7, 8, 9, 10, 11, 12, 13	Select one: ☐ Authored ☒ Approved
Signature: Martha Donoghue -S Digitally signed by Martha Donoghue -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000339007, cn=Martha Donoghue -S Date: 2020.11.25 09:52:53 -05'00'				

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

/s/

NORMA S GRIFFIN
11/25/2020 02:58:36 PM

MARC R THEORET
11/25/2020 03:22:24 PM

My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.