CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761119Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: February 18, 2020

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: BLA 761119 (Vyepti, eptinezumab, ALD-430)

BLA 761119 was submitted by Lundbeck Seattle BioPharmaceuticals, Inc. on February 21, 2019, to support marketing approval of eptinezumab, a calcitonin gene-related peptide (CGRP) receptor antagonist, for the "preventive treatment of migraine in adults." Clinical development of eptinezumab for the proposed indication was conducted by Lundbeck under IND 114647.

Nonclinical studies submitted to the BLA include pharmacology (primary, secondary) and general toxicology (acute IV in rat and monkey; 28-day IV in rat and monkey; 6-month IV in monkey) studies and a standard battery of reproductive and developmental toxicology studies (rat and rabbit). (A chronic toxicity study in a second species (rat) and rodent carcinogenicity studies were not required, primarily because of data demonstrating development of anti-drug antibodies in rat that precluded conduct of meaningful long-term studies.) These studies were reviewed by Dr. Siarey (Pharmacology/Toxicology NDA Review and Evaluation, BLA 761119, Richard Siarey, Ph.D., February 10, 2020). (Dr. Siarey's review references those conducted by Drs. D. Charles Thompson and Edmond Nesti under IND 114647.) Based on the review, Dr. Siarey concludes the nonclinical data are adequate and support approval of the BLA.

Pharmacology

Eptinezumab is a humanized monoclonal IgG_1 antibody that targets both α- and β-CGRP. In vitro binding and functional assays demonstrated pharmacological activity in human, rat, rabbit, and cynomolgus monkey. (In vitro binding data were not provided for monkey because of identical amino acid sequences in human and monkey for both CGRP isoforms.)

SPECIES	BINDING (K_D, nM)		cAMP ACCUMULATION (EC_{50}, nM)	
	α-CGRP	β-CGRP	α-CGRP	β-CGRP
human	0.015	0.057	1.43	0.91
rat	0.170	0.0084	0.55	1.05
rabbit	1.50	0.250	0.12	0.06

Eptinezumab demonstrated no cross-reactivity to other members of the gene family (adrenomedullin, adrenomedullin2/intermedin, amylin, or calcitonin).

Safety pharmacology and PK/TK analyses were incorporated into general toxicology studies.

Toxicology

Non-GLP acute IV toxicity studies were conducted in Sprague-Dawley rat (0, 10, 30, and 100 mg/kg) and cynomolgus monkey (0, 5, 10, 30, and 100 mg/kg). No toxicity was observed in either species.

Pivotal (GLP) toxicity studies were conducted in the same species/strain. In rat, only a 28-day IV toxicity study was conducted. Doses of 0, 10, 30, and 100 mg/kg Q2W produced no toxicity; plasma exposures at the high dose were 3429 µg/mL and 272050 µg*hr/mL for C_{max} and $AUC_{(0\text{-}7d)}$, respectively. In monkey, eptinezumab was tested in 28-day (0, 10, 30, and 100 mg/kg IV Q2W) and 6-month (0, 20, 50, and 150 mg/kg Q2W) studies. No product-related toxicity was evident in the 28-day study. In the 6-month study, death of one low-dose female was attributed to AND-mediated anaphylaxis, which was not considered relevant to human. Plasma exposures at the highest doses tested were 4623 µg/mL and 445733 µg*hr/mL for C_{max} and $AUC_{(0\text{-}7d)}$, respectively, in the 28-day study and 12900 µg/mL and 1290000 µg*hr/mL for C_{max} and $AUC_{(0\text{-}14d)}$, respectively, in the 6-month study. The exposures achieved in the 6-month study provide an adequate safety margin compared to that achieved in humans at the maximum proposed human dose of 300 mg/day (114 µg/mL and 69630 µg*hr/mL for C_{max} and $AUC_{(0\text{-}t)}$, respectively; sponsor's Summary of Clinical Pharmacology Studies, Study ALD403-CLIN-005).

Reproductive and developmental toxicology

A standard battery of reproductive and developmental toxicology studies was conducted in Sprague-Dawley rat (fertility and early embryonic development, embryofetal development (EFD), and pre- and postnatal development) and New Zealand White rabbit (EFD).

In the fertility study, eptinezumab (0, 75, and 150 mg/kg IV QW) was administered to male and female rats prior to and during mating and continuing in females to gestation day (GD) 3-4. The same doses were used in the EFD and pre- and postnatal studies in rat and in the EFD study in rabbit. In the EFD studies, eptinezumab was administered IV on GDs 6, 12, and 18 in rat and on GDs 7, 13, and 20 in rabbit. In the pre- and postnatal development study in rat, eptinezumab was administered IV on GDs 6, 12, and 18 and LDs 4, 10, 16, and 20. No adverse effects were observed. The higher dose tested (150 mg/kg) was the NOAEL in dams, fetuses, and offspring. Plasma exposure data at 150 mg/kg (collected in the pivotal EFD studies) were limited to mean concentrations at 5 min postdose: 4473 and 4116 µg/mL in rat and rabbit, respectively. Therefore, safety margins for labeling must rely on interspecies comparisons based on dose (mg/kg).

Recommendation

The nonclinical studies conducted by the sponsor are adequate to support approval of the BLA for the proposed indication. To support clinical studies under PREA, the sponsor planned to conduct a juvenile animal toxicology study (Agreed iPSP Agreement letter, December 21, 2018); however, the study report has not been submitted. The study should be completed as a post-marketing requirement.

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/s/

LOIS M FREED
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	761-119
Supporting document/s:	001
Serial number:	0001
Applicant's letter date:	February 21, 2019
CDER stamp date:	February 21, 2019
Product:	Vyepti™ (Eptinezumab)
Indication:	Migraine
Applicant:	Alder Biopharmaceuticals Inc.
Review Division:	Division of Neurology 2
Reviewer:	Richard Siarey
Supervisor:	Lois Freed
Acting Division Director:	Nicholas Kozauer
Project Manager:	Lana Chen

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1 Executive Summary

1.1 Introduction

ALD403 (eptinezumab) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that inhibits the calcitonin gene-related peptide (CGRP) by binding to the α- and β-forms of rat, rabbit, cynomolgus monkey, and human CGRP. During a migraine attack, plasma levels of CGRP increase and lead to secretion of vasoactive, proinflammatory, and neurosensitizing mediators. The sponsor has developed eptinezumab for the preventive treatment of migraine.

1.2 Brief Discussion of Nonclinical Findings

Eptinezumab has high affinity and specificity for rat, rabbit, monkey, and human α- and β-CGRP without off target binding to amylin, calcitonin, adrenomedulin, or intermedin/ adrenomedulin-2. In rat, rabbit, and monkey models of dermal blood flow, eptinezumab (IP, IV, and/or SC) reduced the capsaicin- or intradermal β-CGRP-induced increase in dermal blood flow. Nonclinical studies of IV eptinezumab consisted of general toxicology studies in rat and monkey, which included safety pharmacology assessments, a rat fertility study, rat and rabbit embryofetal development studies, and a rat pre- and postnatal development study. The Division agreed that only a monkey chronic (6-month) study was needed (email correspondence, April 4, 2013). No adverse effects of IV eptinezumab were observed in either the rat 4-week or monkey 6-month general toxicology studies; the NOAELs were determined to be 100 mg/kg/week and 150 mg/kg every 2 weeks, respectively. No adverse effects of IV eptinezumab were observed in any of the reproductive and development studies. The NOAEL was 150 mg/kg/week in the rat fertility, rat and rabbit embryofetal development, and rat pre- and postnatal studies. The Division accepted the justification from the sponsor not to conduct carcinogenicity studies (DARRTs IND 114,647; January 27, 2016). Overall, no adverse findings were observed in the toxicology studies.

1.3 Recommendations

1.3.1 Approvability

The nonclinical BLA package supports approval of eptinezumab.

1.3.3 Labeling

Rat and rabbit margins, in the label, appear to be calculated using a body weight of (b) (4) Safety margins need to be calculated using 60 kg as the human body weight.

2 Drug Information

2.1 Drug

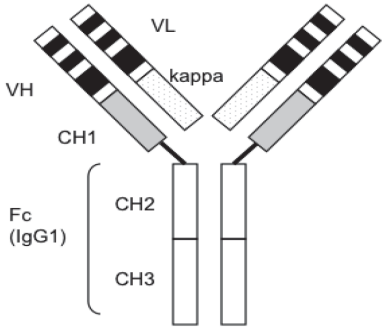
Generic Name: Eptinezumab

Code Name: ALD403

Chemical Name: Immunoglobulin G1, anti-(calcitonin gene-related peptide) (human-Oryctolagus cuniculus monoclonal ALD403 heavy chain), disulfide with human-Oryctolagus cuniculus monoclonal ALD403 κ-chain, dimer (Sponsor's description).

Molecular Formula/Molecular Weight: $C_{6352}H_{9838}N_{1694}O_{1992}S_{46}$/143,283 Daltons

Structure or Biochemical Description: Schematic diagram of eptinezumab from the sponsor



Pharmacologic Class: Anti-CGRP humanized monoclonal antibody

2.2 Relevant INDs, NDAs, BLAs, and DMFs

IND 114,647 (DNP, prevention of migraine).

2.3 Drug Formulation

(b) (4) The drug substance (100 mg/mL) is a sterile, nonpyrogenic, aqueous solution formulated in L-histidine, L-histidine monohydrochloride, sorbitol, polysorbate 80, pH 5.8, and is stored at (b) (4)°C.

2.4 Comments on Novel Excipients

There are no novel excipients, and all inactive ingredients in the drug product formulation meet compendial requirements.

2.5 Comments on Impurities/Degradants of Concern

The CMC reviewer noted that (b) (4) in the final drug substance (corresponding to (b) (4)). The sponsor states that a 2-week bolus IV study (№ (b) (4)-TOX) qualifies (b) (4) however, a 2-week study is not long

enough to qualify chronic dosing. (b) (4) is present at less than the qualification threshold (b) (4), but as the level of (b) (4) per dose is greater than the (b) (4) µg/day limit for individual impurities and whether (b) (4) had a genotoxic structural alert is unknown, a calculation of lifetime intake was performed. The proposed dosing regimen for eptinezumab is once every 3 months; therefore, a comparison with cumulative lifetime limit ((b) (4) can be conducted to confirm that the exposure to (b) (4) is at an acceptable limit.

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population for eptinezumab is individuals that have migraine. The MHRD is 300 mg IV, administered as a 30-min infusion, every 3 months.

2.7 Regulatory Background

A pre-IND meeting for IND 114,647 was held with the sponsor on May 3, 2012 (meeting minutes, June 1, 2012). The original IND was received on December 14, 2012, and allowed to proceed (Agency Letter, February 8, 2013). An EoP2 meeting between the sponsor and FDA was held on October 13, 2016 (see Meeting Minutes, November 2, 2016). A pre-BLA meeting between the sponsor and FDA was held on September 5, 2018 (see Meeting Minutes, October 4, 2018).

3 Studies Submitted

3.1 Studies Reviewed

Reproductive and Developmental

- Study №: ALD403-073-TOX. A fertility and early embryonic development to implantation study of ALD403 by intravenous injection in rats.
- Study №: ALD403-062-TOX. A dosage range-finding embryo-fetal development study of ALD403 by intravenous injection in rats.
- Study №: ALD403-071-TOX. An embryo-fetal development study of ALD403 by intravenous injection in rats.
- Study №: ALD403-063-TOX. A dosage range-finding embryo-fetal development study of ALD403 by intravenous injection in rabbits.

- Study №: ALD403-072-TOX. An embryo-fetal development study of ALD403 by intravenous injection in rabbits.
- Study №: ALD403-085-TOX. A pre and postnatal study of ALD403 by intravenous injection in rats.

3.3 Previous Reviews Referenced

- Pharmacology/Toxicology Review IND 114,627, D.C. Thompson, March 11, 2013
- Pharmacology/Toxicology Review, IND 114,627, D.C. Thompson, February 1, 2016
- Pharmacology/Toxicology Review, IND 114,627, E.D. Nesti, August 16, 2016

4 Pharmacology

Eptinezumab binding affinity to rat, rabbit, and human α- and β-CGRP were determined to be in the pM-nM range (see table below).

Table: Binding affinity of eptinezumab for α- and β-CGRP in different species (Sponsor's)

Species (CGRP)[1]	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (M)
Human-α	3.2E+05	5.0E-06	1.5E-11
Human-β	1.4E+05	5.9E-06	5.7E-11
Rat-α	3.9E+05	6.4E-05	1.7E-10
Rat-β	5.8E+05	5.1E-06	8.4E-12
Rabbit-α	2.5E+05	3.8E-04	1.5E-09
Rabbit-β	5.5E+05	1.4E-04	2.5E-10

1 Cynomolgus monkey was not tested as it has the same amino acid sequence as humans.

In in vitro assays, eptinezumab functionally antagonized α- and β-CGRP-induced accumulation of intracellular cAMP. This was observed in rat myoblast L6 cells using rat α- and β-CGRP and in human neuroepithelioma SK-N-MC cells using rabbit and human α- and β-CGRP (see table below).

Table: Half maximal effective (EC_{50}) and half maximal inhibitory (IC_{50}) concentrations of eptinezumab on CGRP-driven intracellular cAMP accumulation in different species (Sponsor's)

CGRP Species	EC_{50} (nM)	IC_{50} (nM)[1]
Human-α	1.43 (± 0.07)	1.72 (± 0.40)
Human-β	0.91 (± 0.22)	1.55 (± 0.24)
Rat-α	0.55 (± 0.02)	0.34 (± 0.18)
Rat-β	1.05 (± 0.65)	0.43 (± 0.15)
Rabbit-α	0.12 (± 0.004)	1.44 (± 0.48)
Rabbit-β	0.06 (± 0.007)	1.28 (± 0.17)

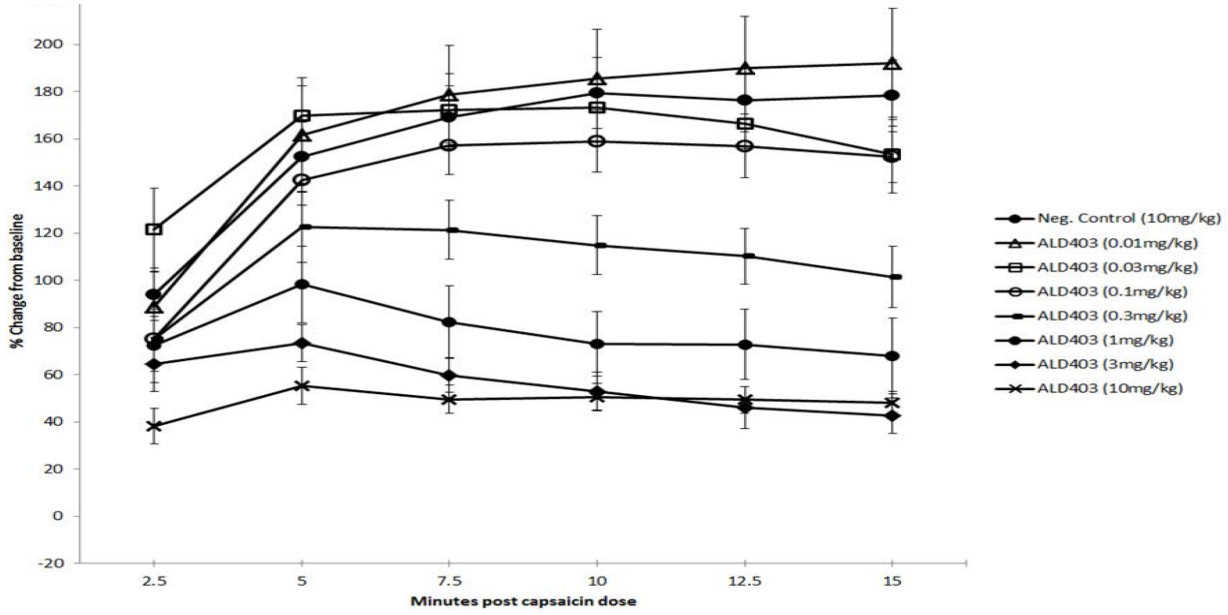
[1] CGRP concentrations used in the assay: human α-CGRP: 6.7 nM; human β-CGRP: 6.7 nM; rabbit α-CGRP: 2.6 nM; rabbit β-CGRP: 2.6 nM; rat α-CGRP: 1.3 nM; rat β-CGRP: 2.7 nM.

An assessment of the ability of eptinezumab to inhibit peptide targets similar to CGRP (amylin, calcitonin, adrenomedulin, and intermedin/adrenomedulin-2) demonstrated no binding of eptinezumab at these targets.

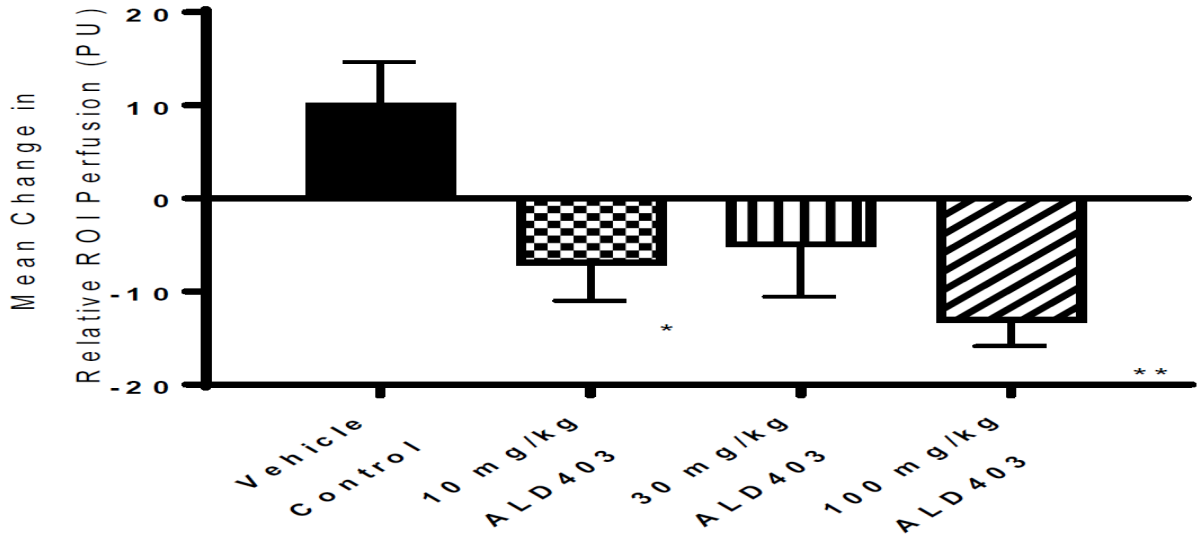
Eptinezumab reduced topical capsaicin-induced increase in dermal blood flow in rats and cynomolgus monkeys and intradermal β-CGRP-induced increase in dermal blood flow in rabbits. Effective doses of eptinezumab were 0.1-30 mg/kg IP in rats, 10-100 mg/kg IV in rabbits, and 30 mg/kg IV and 30-100 mg/kg SC in monkeys.

Figure: Effects of eptinezumab on capsaicin or β-CGRP induced increase in skin blood flow (Sponsor's)

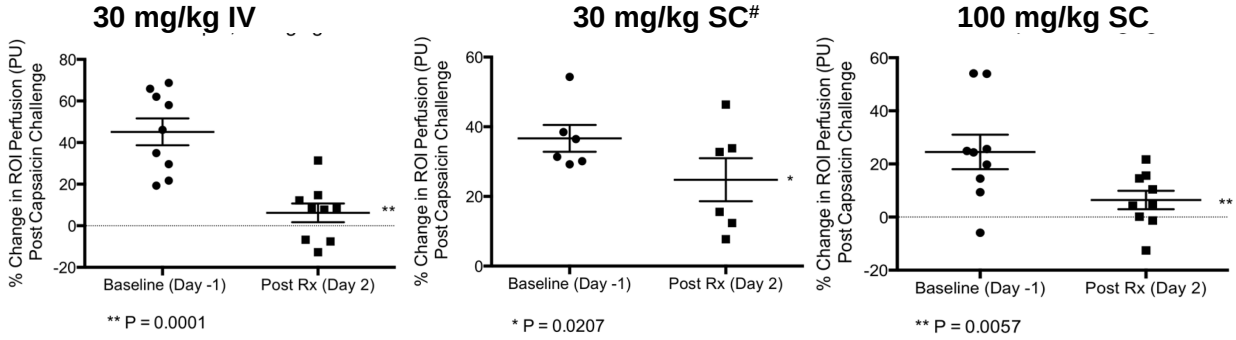
Rat



Rabbit



Monkey



 # animal 3003 excluded

4.3 Safety Pharmacology

No standalone safety pharmacology studies were conducted. Neurological (Studies ALD403-003-TOX, ALD403-004-TOX, ALD403-014-TOX, ALD403-015-TOX, and ALD403-055-TOX), cardiovascular (Studies ALD403-003-TOX, ALD403-015-TOX, and ALD403-055-TOX), and respiratory (ALD403-015-TOX) endpoints were evaluated in single and repeat dose toxicology studies, although an FOB, or equivalent was not conducted and only respiratory rate evaluated. Eptinezumab had no effect on the neurological, cardiovascular, and respiratory systems when given up to 100 mg/kg/week or on the neurological and cardiovascular systems at up to 150 mg/kg once every 2 weeks.

(Summarized from Pharmacology/Toxicology IND Review and Evaluation, IND 114,647, Thompson, March 11, 2013 and February 1, 2016)

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No standalone pharmacokinetic studies were conducted. The toxicokinetic profile of eptinezumab was characterized in the general toxicology studies (studies ALD403-004-TOX, ALD403-003-TOX, ALD403-014-TOX, ALD403-015-TOX, ALD403-055-TOX, and reproductive/developmental toxicology studies in rats and rabbits). Eptinezumab serum concentrations were measured in rat, rabbit, and monkey using either an electrochemiluminescense or ELISA assay. The $t_{½}$ of eptinezumab ranged from 200 to 264 hours in rats and 151 to 299 hours in cynomolgus monkeys. The sponsor stated that distribution of eptinezumab is limited to the vascular compartment, consistent with the general PK of biologics, and metabolism is expected to proceed via proteolysis with incorporation into the endogenous amino acid pool.

6 General Toxicology

6.1 Single-Dose Toxicity

6.1.1 Previously reviewed studies

Rat studies

- **A single dose range-finding study of ALD403 by intravenous bolus injection in Sprague-Dawley rats followed by 14-Days recovery (Study No. ALD403-004-TOX; DARRTs, IND 114,647; Thompson review March 11, 2013); 0, 10, 30, and 100 mg/kg, n = 6/sex/group.**
  Summary: Findings included 1 MDM death on Day 4 and 1 HDF death on Day 1 shortly after dose administration. Clinical signs, clinical pathology, and histopathology findings did not suggest a relationship between the deaths and eptinezumab treatment; however, the proximity of the death in the HDF to dosing suggests that an association cannot be ruled out. Otherwise, drug-related

adverse effects were not observed. Plasma exposure to eptinezumab was comparable between M and F and increased in a generally dose-proportional fashion. The HD (100 mg/kg) was considered the NOEL associated with plasma exposure ($AUC_{0\text{-}336h}$) of 203,424 and 164,289 µg*h/mL in M and F, respectively.

Table: Eptinezumab toxicokinetic data (Sponsor's)

			Day 1						
	Group	Dose Level	Tmax	Cmax		AUC(0-t)		AUC(0-inf)	T1/2
Gender	No.	(mg/kg)	(h)	(µg/mL)	SE	(µg•h/mL)	SE	(µg•h/mL)	(h)
Males	2	10	0.017	302	85.2	24998	2999	28205	120
	3	30	0.017	774	44.8	67822	4494	81448	138
	4	100	0.017	2629	101	203424	22437	226313	105
Females	2	10	0.017	301	30.3	21102	658	26351	155
	3	30	0.017	770	25.6	72479	5320	RNR	RNR
	4	100	0.017	2313	69.6	164289	18818	180871	102

RNR = Result not reported because the AUC(0-inf) was extrapolated by more than 20% or Rsq was <0.800.

Monkey studies

- **A single dose tolerability study of ALD403 by intravenous bolus injection in Cynomolgus monkeys with a 28 day recovery period (Study No. ALD403-003-TOX; DARRTs IND 114,647; Thompson review March 11, 2013); 0, 5, 10, 30, and 100 mg/kg, n = 1/sex/group.**
  Summary: No deaths and no drug-related effects on clinical signs, body weights, food consumption, ECG, hematology, clinical chemistry, and urinalysis were evident. No histopathological assessment was conducted as animals were released back to the test facility colony. Plasma exposure to eptinezumab was comparable between M and F and generally increased in a dose-proportional manner between 5 and 100 mg/kg. The HD (100 mg/kg) was considered the NOEL, which was associated with plasma exposure ($AUC_{0\text{-}648h}$) of 456,838 and 507,371 µg*h/mL in M and F, respectively.

Table: Eptinezumab toxicokinetic data (Sponsor's)

				Day 1									
	Group	Animal	Dose Level	Tmax	Cmax	AUC(0-t)	AUC(0-inf)	T1/2	Vd	CL			
Gender	No.	No.	(mg/kg)	(h)	(µg/mL)	(µg•h/mL)	(µg•h/mL)	(h)	(mL/kg)	(mL/h/kg)	Cmax/D	AUC(0-t)/D	AUC(0-inf)/D
Males	2	2001	5	0.25	127	24618	28796	231	57.9	0.174	25.3	4924	5759
	3	3001	10	0.25	248	50514	63056	280	64.0	0.159	24.8	5051	6306
	4	4001	30	0.25	873	168199	RNR	RNR	RNR	RNR	29.1	5607	–
	5	5001	100	0.25	2332	456838	471986	149	45.6	0.212	23.3	4568	4720
Females	2	2501	5	4	114	24283	30165	276	65.9	0.166	22.7	4857	6033
	3	3601	10	0.25	245	51591	RNR	RNR	RNR	RNR	24.5	5159	–
	4	4501	30	0.25	723	153964	RNR	RNR	RNR	RNR	24.1	5132	–
	5	5501	100	0.25	2284	507371	RNR	RNR	RNR	RNR	22.8	5074	–

RNR Result not reported because the AUC(0-inf) was extrapolated by more than 20% or Rsq was <0.800.

– Not calculated.

6.2 Repeat-Dose Toxicity

6.2.1 Previously reviewed studies

Rat studies

- **A 4-Week study of ALD403 by intravenous bolus injection in Sprague-Dawley rats with a 6-Week recovery period (Study No. ALD403-014-TOX; DARRTs, IND 114,647; Thompson review March 11, 2013); 0, 10, 30, and 100 mg/kg/week.**

  Summary: Findings included 2 premature deaths in TK groups (1 control M and 1 MDF on Days 56 and 3, respectively). The control M death was undetermined and clinical signs (recumbent and dyspneic immediately after blood collection) and gross necropsy observations (expanded lung lobe and thoracic hemorrhage) observed in the MDF suggested a blood collection injury; therefore, these deaths were not considered to be drug-related. Mean body weight in LDM was decreased by 14% at the end of the study compared with the control M, this observation appeared to correlate with reduced food consumption. Microscopic findings included mild to moderate seminiferous tubule degeneration and atrophy in 1 control M and in HDM at the end of both dosing (n = 2) and recovery periods (n = 1); LDM and MDM were not evaluated. Anti-eptinezumab antibodies were detected in all drug-treated groups during the dosing and recovery periods. Anti-eptinezumab antibodies presence appeared to correlate with decreased plasma exposure of eptinezumab, although this was more apparent in LDF and MDF during the dosing period (see tables below). The original reviewer decided that a NOAEL could not be determined in M because of adverse HDM reproductive tract findings coupled with lack of data for LDM and MDM; however, as moderate degeneration and atrophy were also observed in 1 control M this reviewer accepts the sponsors determination that this finding was not an issue and the NOAEL in M was the HD. Therefore, the NOAEL was determined to be 100 mg/kg/week, which was associated with plasma exposure ($AUC_{0\text{-}168h}$) to eptinezumab on Day 22 of 285,574 and 258,526 µg*h/mL in M and F, respectively.

Table: Eptinezumab toxicokinetic data (Sponsor's)

Text Table 15
Toxicokinetic Parameters of ALD403
Day 1

	Group	Dose Level	Tmax	Cmax		AUC(0-t)		AUC(0-168)	AUC(0-inf)	T1/2
Gender	No.	(mg/kg/dose)	(h)	(µg/mL)	SE	(µg•h/mL)	SE	(µg•h/mL)	(µg•h/mL)	(h)
Males	6	10	0.25	247	14.9	13390	967	13390	RNR	RNR
	7	30	0.25	637	55.4	49132	2061	49132	RNR	RNR
	8	100	1	2302	241	143613	6280	143613	RNR	RNR
Females	6	10	1	215	16.7	14119	898	14119	RNR	RNR
	7	30	1	716	60.3	50400	1395	50400	RNR	RNR
	8	100	0.25	2089	92.1	140828	6174	140828	RNR	RNR

Day 22

Gender	Group No.	Dose Level (mg/kg/dose)	Tmax (h)	Cmax (µg/mL)	SE	AUC(0-t) (µg•h/mL)	SE	AUC(0-168) (µg•h/mL)	AUC(0-inf) (µg•h/mL)	T1/2 (h)
Males	6	10	1	390	27.7	61193	12075	26271	RNR	RNR
	7	30	0.25	964	54.9	172297	36475	73698	180537	260
	8	100	1	3481	207	585039	99424	285574	612614	264
Females	6	10	0.25	497	72.7	68258	10847	31280	69520	217
	7	30	0.25	975	236	189277	54508	83220	191317	200
	8	100	1	3376	646	574298	142055	258526	599321	254

RNR = Result not reported because the AUC(0-inf) was extrapolated by more than 20% or Rsq was <0.800.

Table: Eptinezumab toxicokinetic data compared with anti-eptinezumab antibody data (Sponsor's)

		Group 2: 10 mg/kg/week - Concentration (µg/mL)															
		Males															
	Nominal	Main Study Animals										Recovery Animals					
	Time	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	
Occasions	(h)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Mean ± SD
Day 29	n/a	203+	141	152	144+	133	153	200	177	187	Ns	-	-	-	-	-	165 ± 26.4
Day 71	n/a	-	-	-	-	-	-	-	-	-	-	BLLOQ+	BLLOQ+	18.7	29.4	BLLOQ+	9.61 ± 13.7

		Females															
	Nominal	Main Study Animals										Recovery Animals					
	Time	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	
Occasions	(h)	2501	2502	2503	2504	2505	2506	2507	2508	2509	2510	2511	2512	2513	2514	2515	Mean ± SD
Day 29	n/a	161	208	207+	111+	3.44+	131+	2.12+	60.9+	143	0.269+	-	-	-	-	-	103 ± 81.6
Day 71	n/a	-	-	-	-	-	-	-	-	-	-	8.13	Ns	29.4+	BLLOQ	BLLOQ+	9.39 ± 13.9

		Group 3: 30 mg/kg/week - Concentration (µg/mL)															
		Males															
	Nominal	Main Study Animals										Recovery Animals					
	Time	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	
Occasions	(h)	3001	3002	3003	3004	3005	3006	3007	3008	3009	3010	3011	3012	3013	3014	3015	Mean ± SD
Day 29	n/a	359+	403	475+	560	468+	307+	423	435	Ns	362	-	-	-	-	-	421 ± 75.4
Day 71	n/a	-	-	-	-	-	-	-	-	-	-	12.5+	0.735+	37.7+	20.3+	99.1	34.1 ± 38.7

		Females															
	Nominal	Main Study Animals										Recovery Animals					
	Time	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	
Occasions	(h)	3501	3502	3503	3504	3505	3506	3507	3508	3509	3510	3511	3512	3513	3514	3515	Mean ± SD
Day 29	n/a	387	474	12.8+	307+	9.94+	39.9+	0.187+	434	382+	303+	-	-	-	-	-	235 ± 196
Day 71	n/a	-	-	-	-	-	-	-	-	-	-	BLLOQ+	4.48+	23.1+	34.8	0.104+	12.5 ± 15.7

		Group 4: 100 mg/kg/week - Concentration (µg/mL)															
		Males															
	Nominal	Main Study Animals										Recovery Animals					
	Time	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	
Occasions	(h)	4001	4002	4003	4004	4005	4006	4007	4008	4009	4010	4011	4012	4013	4014	4015	Mean ± SD
Day 29	n/a	1399	1568	1199	1179	1139+	1581	1827	0.543+	1522	1210+	-	-	-	-	-	1262 ± 497
Day 71	n/a	-	-	-	-	-	-	-	-	-	-	128	85.2	240+	156	131	148 ± 57.4

		Females															
	Nominal	Main Study Animals										Recovery Animals					
	Time	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	Animal	
Occasions	(h)	4501	4502	4503	4504	4505	4506	4507	4508	4509	4510	4511	4512	4513	4514	4515	Mean ± SD
Day 29	n/a	2628	2192	1899	1881	1985+	1138+	979+	3230+	1064+	3279+	-	-	-	-	-	2027 ± 834
Day 71	n/a	-	-	-	-	-	-	-	-	-	-	BLLOQ+	88.4+	123+	BLLOQ+	BLLOQ	42.3 ± 59.2

BLLOQ = Below the lower limit of quantitation (LLOQ = 0.00500 µg/mL). The BLLOQ concentrations were assigned a value of zero.
Ns No sample collected due to technical difficulties.
n/a Not applicable.
+ Sample tested positive for Anti-drug Antibodies (ADA).
- Sample not collected.

Monkey studies

- **A 28-Day GLP repeat dose study of ALD403 by intravenous bolus injection in Cynomolgus monkeys with a 6 Week recovery period (Study No. ALD403-015-TOX; DARRTs IND 114,647; Thompson review March 11, 2013); 0, 10, 30, and 100 mg/kg/week.**
  Summary: Findings included decreased body weight gain in HDM (0.04 kg; 60%) and HDF (0.02 kg; 50%) compared to control M (0.1 kg) and F (0.04 kg).

No notable microscopic findings were noted apart from perivasculitis/vasculitis in the uterus (minimal) and cervix (mild) in 1 HDF at the end of dosing and mild perivasculitis/vasculitis in the cervix of 1 LDF. Anti-eptinezumab antibodies were detected in all drug-treated groups (2/10, 3/10, and 2/10 animals at the LD, MD, and HD, respectively), but decreased plasma exposure was observed in only 1 MDM. The NOAEL was determined to be the HD (100 mg/kg/week), which was associated with plasma exposures ($AUC_{0\text{-}168h}$) to eptinezumab on Day 22 of 458,826 and 432,640 µg*h/mL in M and F, respectively.

Table: Eptinezumab toxicokinetic data (Sponsor's)

Dose (mg/kg/week):	0 (Control)		10		30		100	
Number of Animals:	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Toxicokinetics (Mean): ALD403								
C_{max} (µg/mL), Day 1	BLLOQ	BLLOQ	312	285	799	806	2452	2445
C_{max} (µg/mL), Day 22	BLLOQ	BLLOQ	478	585	1362	1261	4597	4649
$AUC_{0\text{-}168}$ (µg·hr/mL), Day 1	BLLOQ	BLLOQ	25592	22640	56178	52561	209322	209599
$AUC_{0\text{-}168}$ (µg·hr/mL), Day 22	BLLOQ	BLLOQ	51912	47876	146529	124543	458826	432640
Anti-drug Antibody (ADA) [a]	NE	NE	0	2	2	1	1	1

[a] Number of animals with specific anti-drug antibody (ADA) titers >50 on one or more occasions during the treatment or recovery periods. There were no differences in ALD403 exposure amongst the animals confirmed positive for the presence of specific ADA and the negative monkeys, except for one 30 mg/kg male on Day 22, which exhibited a reduced exposure compared to Day 1 (highest titer value of 6250 on Day 28 which persisted to Day 70). This animal was therefore excluded from the toxicokinetic interpretation for Day 22.

- **A 6-month repeat dose study of ALD403 by intravenous bolus injection in Cynomolgus monkeys with a 3-month recovery period (Study No. ALD403-055-TOX; DARRTs IND 114,647; Thompson review February 1, 2016); 0, 20, 50, and 150 mg/kg once every 2 weeks.**
  Summary: Findings included 1 LDF death that occurred within approximately 30 minutes post-dose on Day 71 (6th dose) after exhibited an anaphylactoid-like reaction. All other animals survived to scheduled necropsy. Mean body weight gain was greater in HDM (0.44 kg; 83%) compared to control M (0.24 kg), whereas body weight gain was less in HDF (0.19 kg; 57%) compared to control F (0.44 kg). Globulin levels were dose-dependently increased in F (up to 25%) and in M, following the dosing and remained elevated in MDM and HDM at the end of the recovery period. The A/G ratio was correspondingly reduced. Inflammatory cell infiltrates (mononuclear and/or mixed cell), a common background finding in cynomolgus monkeys, were observed in numerous tissues at the end of dosing and the recovery period including bone marrow, brain, pancreas, parathyroid gland, skeletal muscle, skin, spinal cord, and thyroid gland. The effect was generally minimal to mild in severity, but the incidence did appear to be slightly increased in animals exposed to eptinezumab compared to control animals. Anti-eptinezumab antibodies were detected in 5/10 (50%), 5/10 (50%), and 11/14 (79%) animals at the LD, MD, and HD, respectively. Eptinezumab exposure did not decreased after repeated administration and exposure in anti-eptinezumab antibody-positive animals did not differ appreciably from anti-eptinezumab antibody-negative animals. Therefore, the presence of immunoreactive anti-eptinezumab antibodies does not appear to have an overall adverse impact on eptinezumab exposure. The NOAEL was determined to be

the HD (150 mg/kg every 2 weeks), which was associated with plasma exposures (AUC_{0-t}) to eptinezumab on Day 183 of 1,480,000 and 1,020,000 µg*h/mL in M and F, respectively.

Table: Eptinezumab toxicokinetic data (Sponsor's)

Day 1

Dose (mg/kg)	Sex	T_{max}[a] (hr)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng•hr/mL)	$T_{1/2}$ (hr)	CL (mL/hr/kg)	Vd (mL/kg)
20	Female	0.0500 (0.0500 - 0.0500)	492,000 ± 62,000	66,800,000 ± 13,200,000	NC	NC	NC
	Male	0.0500 (0.0500 - 96.0)	938,000 ± 499,000	108,000,000 ± 64,200,000	66.5 ± ID	0.0879 ± ID	8.43 ± ID
	All	0.0500 (0.0500 - 96.0)	739,000 ± 426,000	89,800,000 ± 51,000,000	66.5 ± ID	0.0879 ± ID	8.43 ± ID
50	Female	0.0500 (0.0500 - 24.0)	1,550,000 ± 388,000	180,000,000 ± 24,500,000	NC	NC	NC
	Male	0.0500 (0.0500 - 1.00)	1,430,000 ± 240,000	175,000,000 ± 30,900,000	NC	NC	NC
	All	0.0500 (0.0500 - 24.0)	1,490,000 ± 311,000	178,000,000 ± 26,400,000	NC	NC	NC
150	Female	0.0500 (0.0500 - 96.0)	3,910,000 ± 930,000	561,000,000 ± 127,000,000	NC	NC	NC
	Male	1.00 (0.0500 - 4.00)	3,610,000 ± 655,000	475,000,000 ± 65,500,000	142 ± ID	0.274 ± ID	56.2 ± ID
	All	0.610 (0.0500 - 96.0)	3,760,000 ± 789,000	518,000,000 ± 107,000,000	142 ± ID	0.274 ± ID	56.2 ± ID

Day 85

Dose (mg/kg)	Sex	T_{max}[a] (hr)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng•hr/mL)	$T_{1/2}$ (hr)	CL (mL/hr/kg)	Vd (mL/kg)	R_{AUC}[b]
20	Female	1.00 (0.0500 - 1.00)	881,000 ± 165,000	130,000,000 ± 29,900,000	NC	NC	NC	1.97 ± 0.397
	Male	1.00 (0.0500 - 4.00)	1,050,000 ± 511,000	123,000,000 ± 64,100,000	78.0 ± ID	0.487 ± ID	39.8 ± ID	1.26 ± 0.711
	All	1.00 (0.0500 - 4.00)	976,000 ± 385,000	126,000,000 ± 49,000,000	78.0 ± ID	0.487 ± ID	39.8 ± ID	1.58 ± 0.670
50	Female	1.00 (0.0500 - 4.00)	1,780,000 ± 211,000	277,000,000 ± 79,700,000	86.2 ± ID	0.351 ± ID	43.7 ± ID	1.53 ± 0.355
	Male	1.00 (0.0500 - 1.00)	2,360,000 ± 1,020,000	313,000,000 ± 55,600,000	146 ± ID	0.132 ± ID	27.7 ± ID	1.80 ± 0.225
	All	1.00 (0.0500 - 4.00)	2,070,000 ± 762,000	295,000,000 ± 67,500,000	116 ± ID	0.242 ± ID	35.7 ± ID	1.66 ± 0.315
150	Female	1.00 (0.0500 - 4.00)	5,740,000 ± 1,550,000	842,000,000 ± 398,000,000	78.1 ± ID	0.556 ± ID	58.5 ± ID	1.53 ± 0.765
	Male	1.00 (0.0500 - 1.00)	5,170,000 ± 958,000	729,000,000 ± 149,000,000	140 ± ID	0.260 ± ID	52.7 ± ID	1.53 ± 0.195
	All	1.00 (0.0500 - 4.00)	5,460,000 ± 1,270,000	785,000,000 ± 295,000,000	98.9 ± 40.7	0.457 ± 0.227	56.6 ± 3.68	1.53 ± 0.536

Day 183

Dose (mg/kg)	Sex	T_{max}[a] (hr)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng•hr/mL)	$AUC_{(0-tau)}$ (ng•hr/mL)	$T_{1/2}$ (hr)	CL (mL/hr/kg)
20	Female	2.03 (0.0500 - 12.0)	742,000 ± 124,000	158,000,000 ± 91,700,000	136,000,000 ± 27,200,000	307 ± ID	0.145 ± ID
	Male	0.0500 (0.0500 - 1.00)	591,000 ± 178,000	94,600,000 ± 71,900,000	81,500,000 ± 47,200,000	204 ± 159	0.452 ± 0.447
	All	0.0500 (0.0500 - 12.0)	658,000 ± 167,000	123,000,000 ± 82,900,000	106,000,000 ± 47,100,000	245 ± 137	0.329 ± 0.358
50	Female	4.00 (0.0500 - 24.0)	4,480,000 ± 2,800,000	492,000,000 ± 152,000,000	605,000,000 ± 398,000,000	151 ± 93.5	0.154 ± 0.0421
	Male	4.00 (0.0500 - 4.00)	1,900,000 ± 377,000	353,000,000 ± 253,000,000	297,000,000 ± 66,900,000	353 ± ID	0.137 ± ID
	All	4.00 (0.0500 - 24.0)	3,190,000 ± 2,320,000	422,000,000 ± 210,000,000	451,000,000 ± 314,000,000	232 ± 140	0.147 ± 0.0319
150	Female	4.00 (0.0500 - 96.0)	6,160,000 ± 3,870,000	1,020,000,000 ± 641,000,000	904,000,000 ± 680,000,000	292 ± ID	0.202 ± ID
	Male	4.00 (0.0500 - 12.0)	19,600,000 ± 25,300,000	1,480,000,000 ± 940,000,000	1,610,000,000 ± 1,420,000,000	293 ± ID	0.185 ± ID
	All	4.00 (0.0500 - 96.0)	12,900,000 ± 18,700,000	1,250,000,000 ± 808,000,000	1,290,000,000 ± 1,160,000,000	293 ± 34.4	0.193 ± 0.0259

[a] Median (Min - Max)

[b] R_{AUC} = Day 85 $AUC_{(0-t)}$/ Day 1 $AUC_{(0-t)}$.

NC = Not Calculated

ID = Insufficient Data

8 Carcinogenicity

On December 4, 2015 (IND 114,647, SD 041) the sponsor submitted a request that the Division evaluate the need for carcinogenicity studies for eptinezumab. The Division informed the sponsor, by email on January 27, 2016, that the information provided supported the sponsor's justification not to conduct carcinogenicity studies.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: A fertility and early embryonic development to implantation study of ALD403 by intravenous injection in rats

Study no.:	ALD403-073-TOX
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 5, 2015
GLP compliance:	Yes, OECD
QA statement:	Yes
Drug, lot #, and % purity:	ALD403, lot № 1-FIN-2348, 99.4%

Key Study Findings

- No adverse clinical signs, change in body weight, or effects on estrous cycle, reproductive parameters, or macroscopic findings were observed at any dose.
- The NOAEL for fertility and early embryofetal development was 150 mg/kg/week.

Methods

Doses:	0, 75, and 150 mg/kg
Frequency of dosing:	Weekly
Dose volume:	7.5 mL/kg
Route of administration:	IV slow bolus
Formulation/Vehicle:	(b) (4) Histidine / (b) (4) sorbitol, (b) (4) polysorbate 80 [w/w], pH 5.8
Species/Strain:	Rat/Sprague-Dawley Crl:CD(SD)
Number/Sex/Group:	22
Age:	9-12 Weeks
Weight:	Males - 413-517 g; Females - 211-266 g
Study design:	M were dosed starting 4 weeks prior to mating, during mating until necropsy in Week 9 (9 doses). F were dosed starting 2 weeks prior to mating, during the mating period, and on Days 3 and 4 postcoitum.

Observations and results

Mortality

Observations for mortality and moribundity were conducted twice daily.

One HDF was found dead on GD 3. No adverse clinical signs, effect on body weight, food consumption, or macroscopic findings were noted. Although the death was undetermined, the sponsor considered the death unlikely drug-related as there had been no drug-related deaths or effects observed in previous studies.

Clinical Signs
Detailed observations were conducted on days that body weights were evaluated.

No adverse clinical signs were noted. A dose-dependent increase in incidence of hypersensitivity was observed in M; 9 from 4 control M, 49 from 10 LDM, and 74 from 15 HDM.

Body Weight
Animals were weighed twice weekly from day of randomization until the day of necropsy. Body weights for F were also recorded on GDs 0, 3, 7, 10, and 13.

There were no drug-related effects on body weight in M or F at any dose.

Food Consumption
Food consumption was recorded twice weekly from day of randomization until the day of necropsy, and in F was also recorded on GDs 0-3, 3-7, 7-10, and 10-13.

Food consumption was increased by 7% during the study (Days 0-28) in HDM.

Vaginal cytology
Vaginal cytology was examined daily, and estrous cycles assessed by collecting samples for 14 days before mating and then daily until spermatozoa and/or a copulatory plug were observed.

There were no drug-related effects on the estrous cycle at any dose.

Reproductive performance
One F was placed with 1 M in the same dose group for a maximum of 14 days. F were considered to have mated if spermatozoa were observed in a smear of the vaginal lavage and/or a copulatory plug was observed.

There were no drug-related effects on the mean number of days to mating, the mating index, fertility index, or conception rate at any dose.

Reproductive Parameters
Sperm samples were collected from the vas deferens and motility determined; sperm concentration and morphology were determined from sperm collected from the cauda epididymis. The number of corpora lutea were recorded, implantation sites identified as either a live fetus or early resorption, early resorptions noted, and placentae size, color, and shape recorded. Right testes were collected and prepared for histological examination; spermatogenic cycle assessment was conducted on sections of testes from control M and HDM.

There were no differences in M or F reproductive parameters.

Gross findings
M were sacrificed in Week 9 and F were sacrificed on GD 13, and a necropsy examination conducted.

Enlarged mandibular lymph nodes were observed in 5 LDF and 4 HDF; otherwise, no major macroscopic findings were observed.

Organ weights
The following organs were collected and weighed.

Epididymides Gland, prostate Gland, seminal vesicle	Ovaries Testes[a]

[a] Paired organ weight.

No adverse changes in organ weights were observed.

Histopathology
At necropsy, the right testis from control and HD animals was collected and examined microscopically.

Mild tubular atrophy was observed in 1 of 22 HDM.

9.2 Embryofetal Development

Study title: A dosage range-finding embryo-fetal development study of ALD403 by intravenous injection in rats

Study no:	ALD403-062-TOX
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 25, 2014
GLP compliance:	Yes, OECD
QA statement:	Yes
Drug, lot #, and % purity:	ALD403, Lot № 361.008, 99.5%

Key Study Findings
- There were no drug-related changes in any parameter at any dose.
- The maternal and embryofetal development NOAEL was 150 mg/kg/week. Plasma exposure (C_{5min}) at the HD on GD 18 was 5,082 µg/mL.

Methods

Doses:	0, 75, and 150 mg/kg
Frequency of dosing:	Weekly
Dose volume:	7.5 mL/kg
Route of administration:	IV slow bolus
Formulation/Vehicle:	(b) (4) Histidine / (b) (4) sorbitol, (b) (4) polysorbate 80 [w/w], pH 5.8
Species/Strain:	Rat/Sprague-Dawley Crl:CD(SD)
Number/Sex/Group	
Main:	5 F
Toxicokinetic:	2 F control and 4 F LD and HD
Age:	11-12 Weeks
Weight:	Females - 273-336 g
Study design:	F were dosed on GD 6, 12, and 18 days

Observations and results

Mortality

Observations for mortality and moribundity were conducted twice daily.

No unscheduled deaths occurred in dams.

Clinical Signs

Detailed observations were conducted on days that body weights were evaluated.

No adverse clinical signs were noted.

Body Weight

Body weight recordings were taken on GDs 0, 3, 6, 9, 12, 15, 18, and 21.

No drug-related change in body weight was noted.

Food Consumption

Food consumption recordings were taken on GDs 3-6, 6-9, 9-12, 12-15, 15-18, and 18-21.

A slight increase (6%) in food consumption occurred in HD dams between GDs 6-18.

Necropsy

On GD 21, F were sacrificed, and the reproductive tract removed, placentas examined macroscopically, and a necropsy conducted that included evaluation of the carcass and musculoskeletal system, all external surfaces and orifices, cranial cavity and external surfaces of the brain, and thoracic, abdominal, and pelvic cavities with the associated organs and tissues. The uterus was removed for assessment of fertility parameters. The gravid uterus was weighed.

No notable macroscopic findings or changes in gravid uterine weight were noted.

Cesarean Section Data
Rats were examined for number and distribution of corpora lutea, implantation sites, placentae, live and dead fetus, and early and late resorptions. Fetuses were sexed, weighed, and examined for external findings.

There were no notable differences in numbers of corpora lutea, implantations, pre- and post-implantation losses, or resorptions. No malformations, variations, or changes in fetal body weight were noted.

Toxicokinetics
Maternal blood samples were taken from TK animals on GD 6 at 5 minutes post-dose and on GD 18 pre-dose and at 5 minutes post-dose.

Plasma exposure to eptinezumab was generally dose-proportional and did not accumulate during the dosing period.

Table: Toxicokinetic data of eptinezumab

Time	75 mg/kg/day (µg/mL)	150 mg/kg/day (µg/mL)
Day 6, 5 min post-dose	2,681	5,391
Day 18, pre-dose	307	487
Day 18, 5 min post-dose	2,828	5,082

Detection of anti-eptinezumab antibody in serum
Blood samples were taken from animals prior to dosing on GD 6 and prior to necropsy on GD 21.

Immunoreactive anti-eptinezumab antibodies was observed at scheduled termination (PND 21) in 3 out of 9 LD dams and 3 out of 9 HD dams. Of the dams that tested positive for anti-eptinezumab antibody, 3 were TK animals (1 LD and 2 HD) and had no effect on Day 18 eptinezumab plasma exposure.

Study title: An embryo-fetal development study of ALD403 by intravenous injection in rats

Study no:	ALD403-071-TOX
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 2, 2015
GLP compliance:	Yes, OECD
QA statement:	Yes
Drug, lot #, and % purity:	ALD403, Lot № 1-FIN-1722, 99.4%

Key Study Findings

- Eptinezumab was well tolerated with no embryolethality or teratogenicity.
- The maternal and embryofetal development NOAEL was 150 mg/kg/week. Plasma exposure (C_{5min}) on GD 18 at the HD was 4,606 µg/mL.

Methods

Doses:	0, 75, and 150 mg/kg
Frequency of dosing:	Weekly
Dose volume:	7.5 mL/kg
Route of administration:	IV slow bolus
Formulation/Vehicle:	(b) (4) Histidine / (b) (4) sorbitol, (b) (4) polysorbate 80 [w/w], pH 5.8
Species/Strain:	Rat/Sprague-Dawley Crl:CD(SD)
Number/Sex/Group	
Main:	20 F
Toxicokinetic:	4 F control and 8 F LD and HD
Age:	11-12 Weeks
Weight:	Females - 243-338 g
Study design:	F were dosed on GDs 6, 12, and 18

Observations and results

Mortality

Observations for mortality and moribundity were conducted twice daily.

No unscheduled deaths occurred in dams.

Clinical Signs

Detailed observations were conducted on days that body weights were evaluated.

No adverse clinical signs were noted.

Body Weight

Body weight recordings were taken on GDs 0, 3, 6, 9, 12, 15, 18, and 21.

No drug-related change in body weight was noted.

Food Consumption

Food consumption recordings were taken on GDs 3-6, 6-9, 9-12, 12-15, 15-18, and 18-21.

A slight increase (3%) in food consumption occurred in HD dams between GDs 6-18.

Necropsy

On GD 21, F were sacrificed, and the reproductive tract removed, placentas examined macroscopically, and a necropsy conducted that included evaluation of the carcass and musculoskeletal system, all external surfaces and orifices, cranial cavity and external

surfaces of the brain, and thoracic, abdominal, and pelvic cavities with the associated organs and tissues. The uterus was removed for assessment of fertility parameters. The gravid uterus was weighed.

No notable macroscopic findings or changes in gravid uterine weight were noted.

Cesarean Section Data
Rats were examined for number and distribution of corpora lutea, implantation sites, placentae, live and dead fetus, and early and late resorptions. Fetuses were sexed, weighed, and examined for external findings. A visceral examination was conducted on approximately one-half of each litter. A skeletal examination was conducted on the other half of fetuses.

No notable differences in numbers of corpora lutea, implantations, pre- and post-implantation losses, resorptions, or fetal body weight were noted.

External observations: Malformations included hyperflexion of the hindlimbs in 1 control fetus and 2 LD fetuses and malrotated hindlimbs in 2 LD fetuses and 1 HD fetus. No external variations were observed.

Visceral findings: There were no drug-related visceral variations.

Skeletal findings: There were no drug-related skeletal malformations. The total number of skeletal variations were statistically significant increased at the HD and included increase in ossification of the 7th cervical and incomplete ossification of the femur. However, the sponsor stated the incidence was within historical data range and therefore, can be considered related to biological variation and not drug exposure.

Table: Skeletal variations (Sponsor's)

	Group 1		2		3	
	L/E	F/E	L/E	F/E	L/E	F/E
External (EXT)	20	257	20	277	20	253
Visceral (VIS)	20	130	20	140	20	125
Skeletal (SKE)	20	127	20	138	20	129
Technique of Wilson (WT)	20	130	20	140	20	125
	L/A	F/A	L/A	F/A	L/A	F/A
Skeletal Variants (Total)	18	47	20	66	20	69 **
Skull						
Parietal bone(s) incomplete ossification	4	4	4	8	3	6
Frontal bone(s) incomplete ossification	0	0	0	0	1	1
Interparietal bone incomplete ossification	14	27	14	32	14	34
Supraoccipital bone incomplete ossification	0	0	2	3	1	3
Hyoid bone unossified	4	6	2	2	1	1
Hyoid bone incomplete ossification	6	11	12	21	10	17
Prexailla incomplete ossification	5	6	5	7	6	15
Zygomatix temporal incomplete ossification	1	1	1	1	1	1
Zygomatic maxilla incomplete ossification	0	0	0	0	1	1
Vertebral Column						
Extra presacral vertebra(e)	1	1	0	0	1	1
25 presacral vertebra(e)	0	0	0	0	1	1
Ossification center on 1st lumbar or 14th thoracic vertebra	12	14	10	17	9	13
Ribs						
Ribs(s) incomeplete ossification	1	1	4	4	2	2
Rudimentary 14th rib(s)	0	0	0	0	1	1
Ossification center(s) on 7th cervical vertebra	0	0	1	1	4	7 *
Rudimentary 14th rib with contralateral ossification center	1	1	1	1	1	1
Pelvic Girdle						
Pubic bone(s) incomplete ossification	1	1	1	1	1	3
Ischial bone(s) incomplete ossification	1	1	1	1	1	3
Limbs						
Femur incomplete ossification	4	8	3	6	9	19 *

L/E = Litters examined L/A = Litters affected
F/E = Fetuses examined F/A = Fetuses affected
Significantly different from control group (group 1) value: * - P < 0.05 ** - P < 0.01 *** - P < 0.001 (Fisher's)

Toxicokinetics

Maternal blood samples were taken from TK animals on GDs 6, 12, and 18 pre-dose and at 5 minutes post-dose and on GD 21.

Plasma exposure to eptinezumab was generally dose-proportional and did not accumulate during the dosing period.

Table: Toxicokinetic data of eptinezumab

Time	75 mg/kg/day (µg/mL)	150 mg/kg/day (µg/mL)
Day 6, pre-dose	BLQ	BLQ
Day 6, 5 min post-dose	1,820	3,554
Day 12, pre-dose	428	923
Day 12, 5 min post-dose	2,665	5,190
Day 18, pre-dose	259	432
Day 18, 5 min post-dose	2,313	4,606
Day 21	212	375

Detection of anti-eptinezumab antibody in serum
Blood samples were taken from TK animals on GD 5 and prior to necropsy on GD 21.

Immunoreactive anti-eptinezumab antibodies were observed at scheduled termination (PND 21) in 7 of 28 LD dams and 10 of 27 HD dams. Of the dams that tested positive for anti-eptinezumab antibody, 3 were TK animals (1 LD and 2 HD). However, none of the affected animals tested positive for neutralizing antibodies, and there was no effect on plasma eptinezumab exposure.

Study title: A dosage range-finding embryo-fetal development study of ALD403 by intravenous injection in rabbits

Study no:	ALD403-063-TOX
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 25, 2014
GLP compliance:	Yes, OECD
QA statement:	Yes
Drug, lot #, and % purity:	ALD403, Lot № 361.008, 99.5%

Key Study Findings

- There were no drug-related changes in any parameter at any dose.
- The maternal and embryofetal development NOAEL was 150 mg/kg/week. Plasma exposure (C_{5min}) on GD 20 at the HD was 5,218 µg/mL.

Methods

Doses:	0, 75, and 150 mg/kg
Frequency of dosing:	Weekly
Dose volume:	7.5 mL/kg
Route of administration:	IV bolus
Formulation/Vehicle:	(b) (4) Histidine / (b) (4) sorbitol, 0.015% polysorbate 80 [w/w], pH 5.8
Species/Strain:	Rabbit/New Zealand Hra(NZW)SPF
Number/Sex/Group:	5 F
Age:	5-6 Months
Weight:	Females – 3.1-3.5 kg
Study design:	F were dosed on GD 7, 13, and 20 days

Observations and results
Mortality
Observations for mortality and moribundity were conducted twice daily.
No unscheduled deaths occurred in dams. One HD dam aborted on GD 28 and was sacrificed.

Clinical Signs
Detailed observations were conducted on days that body weights were evaluated.

No adverse clinical signs were noted.

Body Weight
Body weight recordings were taken on GDs 0, 5, 7, 10, 13, 16, 20, 23, 26, and 29.

No drug-related change in body weight was noted.

Food Consumption
Food consumption recordings were taken on daily from GD 5.

No drug-related change in food consumption was noted.

Necropsy
On GD 29, F were sacrificed, the reproductive tract removed, and a necropsy conducted that included evaluation of the carcass and musculoskeletal system, all external surfaces and orifices, cranial cavity and external surfaces of the brain, and thoracic, abdominal, and pelvic cavities with the associated organs and tissues. The uterus was removed for assessment of fertility parameters. The gravid uterus was weighed.

No notable macroscopic findings or changes in gravid uterine weight were noted.

Cesarean Section Data
Rabbits were examined for number and distribution of corpora lutea, implantation sites, placentae, live and dead fetus, and early and late resorptions. Fetuses were sexed, weighed, and examined for external findings.

One HD dam aborted on GD 28 There were no notable differences in numbers of corpora lutea, implantations, pre- and post-implantation losses, resorptions, or fetal body weight and there were no dead fetuses. The malformation of a smaller lower jaw was observed in 1 control fetus. No variations were noted.

Toxicokinetics
Blood samples were taken on GD 7, 13, 17, 20, and 29 at time points in the tables below.

Table: Blood sample collection time points (Sponsor's)
GDs 7, 13, and 20

Group No.	No. of Females	Sample Collection Time Points (Time Postdose)	
		0[a] hr	Immediately post dose
1	5	-	X
2	5	X	X
3	5	X	X

x = Sample collected; - = Not applicable
[a] Sample collected before dosing.

GDs 17 and 29

Group No.	No. of Females	Sample Collection Time Points	
		Day 17 pc[b,]	Day 29 pc[c]
1	5	X	X
2	5	X	X
3	5	X	X

x = Sample collected; - = Not applicable
[b] Sample collected on Day 17 pc at the same time as the post dose sample collection on Day 13 pc
[c] Sample collected on Day 29 pc at the same time as the post dose sample collection on Day 20 pc

Plasma exposure to eptinezumab was generally dose-proportional and did not accumulate during the dosing period.

Table: Toxicokinetic data of eptinezumab

Time	75 mg/kg/day (µg/mL)	150 mg/kg/day (µg/mL)
Day 7, pre-dose	BLQ	BLQ
Day 7, post-dose	2,795	4,365
Day 13, pre-dose	1,067	1,658
Day 13, post-dose	3,566	6,344
Day 17, post-dose	1,552	3,052
Day 20, pre-dose	967	1,095
Day 20, post-dose	3,116	5,218
Day 29, 5 min post-dose	431	219

Detection of anti-eptinezumab antibody in serum

Blood samples were taken from animals prior to dosing on GDs 7, 13, 20 and on GDs 17 and 29.

Immunoreactive anti-eptinezumab antibody was observed in 2 of 5 dams at the LD and all dams at the HD. The LD dams had positive anti-eptinezumab antibody titers that increased from pre-dose (GD 7) to GD 29. Of the 5 HD dams with positive immunoreactive anti-eptinezumab antibody titers, 2 were observed with increasing anti-eptinezumab antibody titers from pre-dose to GD 29, 2 were observed with a transient increase in immunoreactive anti-eptinezumab antibody titers, and 1 tested positive only on GD 29. The presence of anti-eptinezumab antibody appeared to have a minimal decreasing affect the plasma exposure of eptinezumab. Animals testing positive for anti-eptinezumab antibody were not positive for neutralizing antibody activity.

Study title: An embryo-fetal development study of ALD403 by intravenous injection in rabbits

Study no:	ALD403-072-TOX
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 2, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ALD403, Lot № 1-FIN-1722, 99.4%

Key Study Findings

- Eptinezumab was well tolerated with no embryolethality or teratogenicity.
- The maternal and embryofetal development NOAEL was 150 mg/kg/week. Plasma exposure (C_{5min}) on GD 20 at the HD was 4,292 µg/mL.

Methods

Doses:	0, 75, and 150 mg/kg
Frequency of dosing:	Weekly
Dose volume:	7.5 mL/kg
Route of administration:	IV slow bolus
Formulation/Vehicle:	(b) (4) Histidine / (b) (4) sorbitol, (b) (4) polysorbate 80 [w/w], pH 5.8
Species/Strain:	Rabbit/New Zealand Hra(NZW)SPF
Number/Sex/Group	
Main:	20 F
Toxicokinetic:	2 control and 4 LD and HD
Age:	5-6 Months
Weight:	Females: 2.9-3.6 kg
Study design:	F were dosed on GD 7, 13, and 20 days

Observations and Results for Dams

Mortality

Observations for mortality and moribundity were conducted twice daily.

No unscheduled deaths occurred in dams.

Clinical Signs

Detailed observations were conducted on days that body weights were evaluated.

No adverse clinical signs were noted.

Body Weight
Body weight recordings were taken on GDs 0, 5, 7, 10, 13, 16, 20, 23, 26, and 29.

No drug-related change in body weight was noted.

Food Consumption
Food consumption recordings were taken daily from GD 5.

Food consumption was decreased by 7% between GDs 7 and 20 in HDF; otherwise, no notable change in food consumption was noted.

Necropsy
On GD 29, F were sacrificed, the reproductive tract removed, and a complete necropsy conducted. The uterus was removed for assessment of fertility parameters. The gravid uterus was weighed.

No notable macroscopic findings or changes in gravid uterine weight were noted.

Cesarean Section Data
Rabbits were examined for number and distribution of corpora lutea, implantation sites, placentae, live and dead fetus, and early and late resorptions. Fetuses were sexed, weighed, and examined for external, visceral, and skeletal findings.

There were no notable differences in numbers of corpora lutea, implantations, pre- and post-implantation losses, resorptions, or dead fetuses. Mean fetal weights were slight decreased in LD (6%) and HD (7%) fetuses.

External observations: There were no malformations, and incidences of variants were comparable between the groups.

Visceral findings: There were no malformations. There was a slight increase in accessory lung lobes absent in LD (3) and HD (4) fetuses compared to control (1) fetuses; otherwise, incidences of variations were comparable among the groups.

Table: Visceral variations (Sponsor's)

Group 1 - Control Group 2 - ALD403 75 mg/kg/dose
Group 3 - ALD403 150 mg/kg/dose

	Group 1		2		3	
	L/E	F/E	L/E	F/E	L/E	F/E
External (EXT)	20	153	20	164	20	176
Visceral (VIS)	20	153	20	164	20	176
Skeletal (SKE)	20	153	20	164	20	176
	L/A	F/A	L/A	F/A	L/A	F/A
Malformations (Total)	0	0	0	0	0	0
External and Visceral Variants (Total)	2	4	7	7	4	7
Lungs and Thymus						
Accessory lung lobes absent (VIS)	1	1	3	3	2	4
Uterus Ovaries						
Ovarian cyst (VIS)	0	0	0	0	1	1

L/E = Litters examined L/A = Litters affected
F/E = Fetuses examined F/A = Fetuses affected
Significantly different from control group (group 1) value: * - P ≤ 0.05 ** - P ≤ 0.01 *** - P ≤ 0.001 (Fisher's)

Skeletal findings: There were no malformations and apart from an increased occurrence of sternebral variations at the LD, incidences of variations were comparable among groups.

Table: Skeletal variations (Sponsor's)

Group 1 - Control Group 2 - ALD403 75 mg/kg/dose
Group 3 - ALD403 150 mg/kg/dose

	Affected Fetuses/Litters Mean % (SD) Group 1	2	3
Sternebrae (unossified/incomplete/semi-bipartite/ bipartite)	30.25 (25.34)	55.39 D (29.85)	44.90 (35.27)

Significantly different from control group (Group 1) value: D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Toxicokinetics

Blood samples were taken from TK animals on GDs 7, 13, and 20 pre-dose and at 5 minutes post-dose and on GD 29.

Plasma exposure to eptinezumab was generally dose-proportional and did not accumulate during the dosing period.

Table: Toxicokinetic data of eptinezumab

Time	75 mg/kg/day (µg/mL)	150 mg/kg/day (µg/mL)
Day 7, pre-dose	BLQ	BLQ
Day 7, 5 min post-dose	2,009	3,928
Day 13, pre-dose	631	1,120
Day 13, 5 min post-dose	2,572	4,127
Day 20, pre-dose	328	1,035
Day 20, 5 min post-dose	2,173	4,292
Day 29	91	192

Detection of anti-eptinezumab antibody in serum
Blood samples were taken from TK animals prior to dosing on GDs 7, 13, and 20 and on GD 29.

Immunoreactive anti-eptinezumab antibody was observed at scheduled termination in 10 of 24 LD dams and 9 of 24 HD dams. Of the dams that tested positive for the presence of anti-drug antibody on GD 29, 4 were TK dams (3 LD and 1 HD). The presence of anti-eptinezumab antibodies did not appear to affect the plasma exposure of eptinezumab on GDs 7, 13, and 20, as the mean exposure to eptinezumab did not decrease after repeated administration. However, on the day of sacrifice (GD 29) plasma exposure to eptinezumab was 27 and 137 µg/mL at the LD and 56 and 273 µg/mL at the HD in anti-eptinezumab antibody positive and negative animals, respectively. Five of 10 LD dams and 3 of 9 HD dams were positive for neutralizing antibody activity, and the mean plasma exposure to eptinezumab in these dams was lower than dams testing negative for neutralizing antibody activity at both the LD (1 µg/mL compared to 52 µg/mL) and HD (3 µg/mL compared to 83 µg/mL).

9.3 Prenatal and Postnatal Development

Study title: A pre and postnatal study of ALD403 by intravenous injection in rats

Study no: ALD403-085-TOX
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: September 2, 2016
GLP compliance: Yes, OECD
QA statement: Yes
Drug, lot #, and % purity: ALD403, Lot № 1-FIN-2598, 99.5%

Key Study Findings

- There was 1 undetermined F_0 HD dam death; otherwise no notable findings were observed, apart from a slight decrease in food consumption at the HD.

- There was 1 undetermined LDF F_1 pup death; clinical signs observed in F_1 pups included signs of domed skull in 1 HDM and 1 HDF with accumulation of fluid consistent with hydrocephaly noted in the HDM.
- Body weight was slightly increased at all doses in M and F F_1 pups between PND 4-21.
- Malformations noted in 1 HDM F_1 pup was dilated olfactory bulb and ventricles.
- Post weaning no adverse findings were observed in clinical signs, body weight, physical development, behavior, and reproduction in the F_1 animals.
- The NOAEL for toxicity and reproductive performance in F_0 dams and F_1 generation development was 150 mg/kg administered once every 6 days.

Methods

Doses:	0, 75, and 150 mg/kg
Frequency of dosing:	Once every 6 days
Dose volume:	7.5 mL/kg
Route of administration:	IV slow bolus
Formulation/Vehicle:	(b) (4) Histidine / (b) (4) sorbitol, (b) (4) polysorbate 80 [w/w], pH 5.8
Species/Strain:	Rat/Sprague-Dawley Crl:CD(SD)
Number/Sex/Group:	20 control and 30 F LD and HD
Age:	73-87 Days
Weight:	Females - 222-350 g
Study design:	F were dosed on GDs 6, 12, 18, and 24 and Lactation Days 4, 10, 16, and 20

Observations and Results for F_0 Dams

Mortality

Observations were conducted twice daily.

One HD dam was found dead on Lactation Day 15. The cause of death was undetermined. There were no clinical signs prior to death; macroscopic findings included failure for the lung to collapse and pale discoloration of the spleen.

Clinical Signs

Detailed examinations were conducted daily prior to initiation of dosing and on days body weight was evaluated.

No adverse clinical signs were observed in F_0 dams.

Body Weight

Body weight recordings for F_0 dams were taken on GDs 0, 3, 6, 9, 12, 15, 18, and 20 and on Lactation Days 4, 7, 10, 14, 17, and 21.

No drug-related change in body weight was noted.

Food Consumption
Food consumption for F_0 dams were recorded on GDs 3-6, 6-9, 9-12, 12-15, 15-18, and 19-20 and on Lactation Days 0-4, 4-7, 7-10, and 10-14.

Food consumption in HD dams was significantly increased (8%) during lactation.

Reproduction parameters
The time of onset, number of pups (dead and alive), implantation scars, and completion of parturition were recorded, with any sign of dystocia noted.

There was no notable change in reproduction parameters.

Tables: Summary of maternal reproduction parameters (Sponsor's)

Group	No. of Mated Females	No. of Pregnant Females	Pregnancy Rate (%)	Gestation Index (%)	Dead Pups		Malformed Pups	
					Litters Affected	Pups Affected	Litters Affected	Pups Affected
1	20	18	90.0	100.0	3	3	0	0
2	30	30	100.0	100.0	6	9	1	1
3	30	30	100.0	100.0	6	7	1	1

Significantly different from control group (Group 1) value: * - P ≤ 0.05 ** - P ≤ 0.01 *** - P ≤ 0.001 (Fisher's)

Group	Summary Information	Length of Gestation (Days)	Sex Ratio (% Males)	Number of Pups at Birth/Litters			No. of Implant Scars	Live Birth Index (%)
				Live	Dead	Malformed		
1	Mean	21.9	54.63	12.7	0.2	0.0	13.8	91.57
	SD	0.3	11.52	2.3	0.4	0.0	1.5	11.03
	N	18	18	18	18	18	18	18
2	Mean	21.7	48.32	11.9	0.3	0.0	13.2	90.25
	SD	0.5	12.35	2.5	0.7	0.2	2.5	9.31
	N	30	30	30	30	30	30	30
	% Diff (G1)	-1	-12	-6	50		-4	-1
3	Mean	21.6	48.08	12.5	0.2	0.0	13.8	90.43
	SD	0.5	12.81	2.4	0.5	0.2	2.1	10.58
	N	30	30	30	30	30	30	30
	% Diff (G1)	-1	-12	-2	0		0	-1

Significantly different from control group (Group 1) value: D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Necropsy
Necropsy of F_0 dams occurred at scheduled termination after weaning (Lactation Days 21).

There were no notable macroscopic findings in F_0 dams.

Observations and Results for F_1 Generation (pre-weaning)
On PND 4, litters were culled to 8 (4 M and 4 F, where possible) pups per litter. Culled pups were euthanized and the carcasses discarded.

Mortality
Observations for general condition were conducted on F_1 pups twice daily.

There was no effect on pup viability and survival. The pups (4 M and 4 F) from the HD dam found dead on Lactation Day 15 were euthanized.

Clinical Signs
Clinical signs were evaluated in F_1 pups daily during the lactation period.

Between PNDs 19 and 21 signs of a domed skull was observed in 1 HDM and 1 HDF from the same litter; the HDM had accumulation of fluid consistent with hydrocephaly. Fluid accumulation was also observed in another pup in the same litter and 1 control F pup. There was an increase in thin fur in HD F_1 pups.

Body Weight
Body weight recordings for F_1 pups were taken on PNDs 0, 4, 7, 14, 17, and 21.

Litter mean F_1 pup body weight was increased on PNDs 4-21 in M pups by 4% and 6% and in F pups by 3% and 5% at the LD and HD, respectively.

Physical development
Observations and tests were conducted for auricular startle response from PND 12 and negative geotaxis from PND 8. Sexual maturation parameters were assessed in post-weanling animals (see below).

There were no notable changes in the negative geotaxis parameters or on auricular startle response in F_1 pups.

Necropsy
Necropsy was conducted on F_1 pups that were found dead or euthanized between PNDs 0 and 7 and on PND 21 on F_1 pups not selected for mating.

No notable findings were observed in pups found dead (M: 6, 4, and 5 control, LD, and HD, respectively; F: 3, 7, and 4 control, LD, and HD, respectively).

Observations and Results for F_1 Generation (post-weaning)
Placement of F_1 adults (post-weaning animals)
On PND 21, 1 M and 1 F from each litter were selected for further evaluation; 18, 30, and 29 pups/sex were selected for control, LD, and HD groups, respectively. Following blood sample collection for bioanalysis and anti-drug antibody determination, the remaining pups were euthanized on PND 21.

Mortality
Observations for mortality and moribundity were conducted twice daily.

No unscheduled deaths occurred in F_1 adults.

Clinical signs
Detailed examinations were conducted weekly.

No adverse clinical signs were observed in F_1 adults.

Body Weight
Body weight recordings were taken twice weekly after weaning. Mated F_1 F body weight recordings were taken on GDs 0, 3, 7, 10, and 13.

No drug-related change in body weight was noted.

Physical development
Pupillary closure and visual placing responses were tested on PND 21. Vaginal opening was assessed from PND 26 and preputial separation was assessed from PND 35. Righting reflex was tested on Day PND 28.

There was no effect on pupillary closure, visual placing, righting reflex, preputial separation, or vaginal opening.

Behavioral assessment
Tests conducted included motor activity on PND 60 ± 2, auditory startle on PND 55, and Cincinnati water maze (learning and memory) between PNDs 60 and 70. In the Cincinnati water maze, performance (ability to swim) was assessed and learning and memory was assessed using 2 paths.

Motor activity: Motor activity was comparable between eptinezumab-dosed and control groups in M and F.

Auditory startle habituation: Startle habituation was comparable between eptinezumab-dosed and control groups in M and F.

Cincinnati water maze: Swimming ability, completion times, and number of errors in the Cincinnati water maze were comparable between eptinezumab-dosed and control groups in M and F.

Estrous cycle
The estrous cycle was determined by examination of the vaginal lavage for at least 14 days prior to placement for mating, during the mating period, and until the day of confirmed mating.

Estrous cycle length was comparable between eptinezumab-dosed and control F groups.

Reproduction parameters
Mating pairs (1 M and 1 F) were established on PND 85 and cohabitated for up to 21 days. F were examined for evidence of mating. On GD 13, animals were

euthanized, and the reproductive tract examined for number of corpora lutea, implantation sites, number of pups (dead and alive), and resorptions.

Mating and fertility indices, conception rate, mean number of days mating, number of corpora lutea, implantation sites, live and dead embryos, early resorptions, and pre- and post-implantation losses were comparable between eptinezumab-dosed and control groups.

Necropsy
Gross examination was conducted.

No notable macroscopic findings were noted in F_1 adults.

10 Special Toxicology Studies

10.1 Local Tolerance

Local toxicity of eptinezumab was assessed after single (SC) and repeat-dose (4 weekly SC or IM doses) dosing in monkey and rats, respectively. No injection site reactions to eptinezumab were observed, apart from minimal mononuclear cell infiltrate in IM repeat dosing in 5 of 6 HD (100 mg/mL) rats.

(Summarized from Pharmacology/Toxicology IND Review and Evaluation, IND 114,647, Thompson, March 11, 2013 and February 1, 2016, and Nesti, August 16, 2016)

10.2 Tissue Cross-Reactivity

Tissue cross-reactivity of ALD403 with human, Cynomolgus monkey, and rat tissues in vitro (*Study №: ALD403-016-TOX*; **DARRTs, IND 114,647; Thompson review March 11, 2013)**.
The tissue cross-reactivity of eptinezumab (2.5 and 10.0 µg/mL) was assessed in a panel of tissues from Sprague-Dawley rats (n = 3), cynomolgus monkeys (n = 3), and normal humans (n = 3). Staining was generally observed in tissues in blood vessels, endothelium, and adventitia, but binding was observed in more human tissues (31) than rats (9) and monkeys (10). Binding of eptinezumab in human tissues included; bladder, breast, colon, eye, fallopian, lymph node, nerve, ovary, parotid, skin, small intestine, spinal cord, striated muscle, tonsil, ureter, and uterus. Of these tissues; bladder, breast, eye, fallopian, nerve**,** parotid, skin, spinal cord, striated muscle, tonsil, ureter, and uterus, eptinezumab binding was generally negligible at the LD and with low intensity and incidence than at 10 µg/mL eptinezumab. At the time the study was reviewed the sponsor was directed to provide additional information, if possible, on the nature of the specific binding (e.g., localization) to facilitate evaluation of these data. The sponsor reported that the observed pattern of staining with eptinezumab was consistent with the expression of CGRP in tissues (Brain and Grant, Physiol Rev 84: 903-934, 2004) and differences in staining between human and the nonclinical species was due to individual variation and/or differences in age, disease status, death process, or true species

differences. However, the sponsor provided no discussion on the location of the staining in human tissues, whether it was intracellular and therefore irrelevant.

Summary of Incidence and Intensity in Rat Tissues with Specific ALD403 Staining				
Tissue	ALD403 10.0 µg/mL		ALD403 2.5 µg/mL	
	Incidence	Intensity	Incidence	Intensity
GI-Tract-Stomach	3/3	1+ - 2+	0/3	Neg
Heart	3/3	1+ - 2+	0/3	Neg
Liver	3/3	1+	0/3	Neg
Lung	3/3	1+	0/3	Neg
Pancreas	3/3	1+	0/3	Neg
Spleen	1/3	1+	0/3	Neg
Testis	3/3	1+	0/3	Neg
Thymus	2/3	3+	2/3	1+
Thyroid	3/3	1+	0/3	Neg
Incidence: Number of individual tissue sections with specific staining / number of individual tissues evaluated.				

Summary of Incidence and Intensity in Cynomolgus Monkey Tissues with Specific ALD403 Staining				
Tissue	ALD403 10.0 µg/mL		ALD403 2.5 µg/mL	
	Incidence	Intensity	Incidence	Intensity
Adrenal	3/3	1+ - 3+	2/3	1+
Brain-Cerebellum	3/3	1+	0/3	Neg
Brain-Cerebral Cortex	3/3	1+	0/3	Neg
GI-Tract-Stomach	3/3	2+ - 3+	3/3	1+
Heart	3/3	1+	0/3	Neg
Kidney-Glomerulus	2/3	1+	0/3	Neg
Kidney-Tubule	2/3	1+	0/3	Neg
Lung	1/3	2+	0/3	Neg
Pancreas	3/3	1+	1/3	1+
Parathyroid	1/2	1+	0/2	Neg
Prostate	1/3	1+	0/3	Neg
Thyroid	1/3	1+	0/3	Neg
Incidence: Number of individual tissue sections with specific staining / number of individual tissues evaluated.				

Summary of Incidence and Intensity in Human Tissues with Specific ALD403 Staining				
Tissue	ALD403 10.0 µg/mL		ALD403 2.5 µg/mL	
	Incidence	Intensity	Incidence	Intensity
Adrenal	3/3	1+ - 2+	2/3	1+
Bladder	3/3	1+	0/3	Neg
Breast	1/3	2+	0/3	Neg
Brain-Cerebellum	3/3	1+	0/3	Neg
Brain-Cerebral Cortex	3/3	1+	0/3	Neg
Colon	3/3	1+ - 3+	1/3	1+
Eye	2/3	1+	0/3	Neg
Fallopian Tube	1/3	1+	0/3	Neg
GI-Tract-Small Intestine	3/3	2+	2/3	1+
GI-Tract-Stomach	3/3	2+ - 4+	3/3	2+ - 3+
Heart	3/3	1+ - 2+	0/3	Neg
Kidney-Glomerulus	2/3	1+	0/3	Neg
Kidney-Tubule	2/3	1+	0/3	Neg
Liver	3/3	1+ - 2+	3/3	1+
Lung	3/3	1+ - 2+	0/3	Neg
Lymph Node	3/3	1+ - 2+	2/3	1+
Nerve-Peripheral	1/3	2+	1/3	1+
Ovary	3/3	3+	3/3	1+ - 2+
Pancreas	3/3	3+ - 4+	3/3	1+ - 2+
Parathyroid	3/3	2+ - 3+	3/3	1+
Parotid (Salivary) Gland	2/3	2+	0/3	Neg
Prostate	3/3	2+ - 3+	3/3	1+ - 2+
Skin	1/3	1+ (vessels) – 4+ (dermis)	1/3	1+ (vessels) – 2+ (dermis)
Spinal Cord	3/3	1+	0/3	Neg
Spleen	3/3	1+ - 2+	0/3	Neg
Striated Muscle	2/3	1+ - 2+	1/3	1+
Testis	3/3	1+ - 4+	2/3	2+
Thymus	3/3	1+ - 2+	3/3	1+
Thyroid	3/3	1+	0/3	Neg
Tonsil	3/3	2+	2/3	1+
Ureter	2/3	1+	0/3	Neg
Uterus-Cervix	2/3	1+ - 2+	1/3	1+
Uterus-Endometrium	2/3	1+	1/3	1+
Incidence: Number of individual tissue sections with specific staining / number of individual tissues evaluated.				

11 Integrated Summary and Safety Evaluation

Eptinezumab is a human monoclonal antibody that inhibits CGRP by binding to the α- and β-forms of CGRP. During a migraine, plasma levels of CGRP increase and this leads to secretion of vasoactive, proinflammatory, and neurosensitizing mediators. It has been suggested that inhibiting CGRP receptor binding will prevent migraine. The sponsor is proposing to administer eptinezumab once every 3 months for the preventative treatment of migraine.

Eptinezumab has pM-nM affinity for rat, rabbit, and human α- and β-CGRP, without off-target binding to peptide targets similar to CGRP, e.g., amylin, calcitonin, adrenomedulin, and intermedin/adrenomedulin-2. In functional assays in rat myoblast L6 and human SK-N-MC cells, eptinezumab inhibited CGRP accumulation of cAMP, with IC_{50}'s in the low nM range (≤1.8 nM). In in vivo pharmacodynamics studies in rats and monkeys, eptinezumab (0.1-30 mg/kg IP in rats and 30 mg/kg IV and 30-100 mg/kg SC in monkeys) reduced capsaicin-induced increases in dermal blood flow; in rabbit, IV administration of eptinezumab (10-100 mg/kg) inhibited intradermal β-CGRP-induced increases in forearm dermal blood flow.

The pharmacokinetics of eptinezumab were assessed in toxicology studies. The $t_{½}$ of eptinezumab ranged from 200 to 264 hours in rats and 151 to 299 hours in cynomolgus monkeys. The distribution of eptinezumab is expected to be limited to the vascular compartment, consistent with the general pharmacokinetic of biologics, and metabolism is expected to proceed via proteolysis, with incorporation into the endogenous amino acid pool.

In the rat 4-week toxicology study (0, 10, 30, and 100 mg/kg/week IV), the NOAEL was the HD (100 mg/kg/week), which was associated with plasma exposures of 285,574 and 258,526 µg*h/mL in M and F, respectively. The presence of anti-eptinezumab antibodies appeared to correlate with decreased plasma eptinezumab exposure. This was more apparent in LDF and MDF and much less at the HD; therefore, the study was not compromised. A chronic rat toxicology study was not conducted. Rationale for justifying the use of a single species (monkey) for chronic toxicology studies was submitted to IND 114,647 by the sponsor (February 12, 2013; SD005). The Division agreed with the sponsor's proposal to conduct a chronic toxicology study only in monkeys. In the 6-month monkey study (0, 20, 50, and 150 mg/kg/2 weeks IV), 1 LDF died within approximately 30 minutes post-dose on Day 71 (6^{th} dose) after exhibiting an anaphylactoid-like reaction. At the end of dosing and recovery periods, a slight dose-dependent increase in inflammatory cell infiltration was observed in several tissues. The NOAEL was the HD (150 mg/kg/2 weeks), which was associated with plasma exposures of 1,480,000 and 1,020,000 µg*h/mL in M and F, respectively. The presence of anti-eptinezumab antibodies did not appear to have any overall adverse impact on eptinezumab exposure.

Reproductive and development toxicity assessment of IV eptinezumab (0, 75, and 150 mg/kg/week) consisted of a fertility study in rat, embryofetal development studies in rat and rabbit, and a pre- and postnatal development study in rat. In the embryofetal

development studies in rat and rabbit, no drug-related effects were observed; therefore, the NOAEL was the HD, which was associated with plasma exposures (C_{5min}) of 4,606 and 4,292 µg/mL in rats and rabbits, respectively. In the pre- and postnatal development study (0, 75, and 150 mg/kg Q6), no adverse changes were noted; therefore, the NOAEL was the HD.

The Division agreed with the sponsor's justification not to conduct carcinogenicity studies.

In a tissue cross-reactivity study, eptinezumab staining was generally in blood vessels including endothelium, smooth muscle, and adventitia. In local tolerance studies, eptinezumab caused no adverse injection site reactions in rats or monkeys after SC or IM injections.

In conclusion, eptinezumab was shown to have high affinity for α- and β-CGRP and to effectively antagonize CGRP activity. In pharmacodynamics studies, eptinezumab administered to rat, rabbit, or monkey inhibited capsaicin or intradermal β-CGRP-induced dermal blood flow increases. No effect on the neurological, cardiovascular, or respiratory systems was observed in safety pharmacology assessments. No adverse findings were noted in the general toxicity and reproductive and developmental studies. The main finding in the 6-month study in monkeys was inflammatory cell infiltrates in numerous tissues that appeared to be dose-related. Therefore, the submitted nonclinical package supports approval of eptinezumab.

Table of safety margins

Study	Species	Study duration	NOAEL (mg/kg)	Margin based on $AUC_{0\text{-}168h}$*	Margin based on dose#
General toxicology	Rat	4 Weeks	100 mg/kg/week	5-fold	20-fold
	Monkey	6 Months	150 mg/kg/2 week	ND (24-fold+)	30-fold
Embryo-fetal development	Rat	GD 6 to 18	150 mg/kg/week	ND	30-fold
	Rabbit	GD 7 to 20	150 mg/kg/week	ND	30-fold
Pre- and postnatal development	Rat	GD 6 to LD 20	150 mg/kg/week	No TK	30-fold

***AUC in human: 52906 µg*h/ml at 300 mg/day. +calculated from monkey $AUC_{0\text{-}t}$ value (0-2016h). #Maximum recommend dose: 300 mg. ND – not determined**

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/

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02/10/2020 08:20:17 AM

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