CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761142Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

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

Division of Neurology 2
Division of Pharmacology/Toxicology
Office of Neuroscience
Center for Drug Evaluation and Research

Date: June 1, 2020

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

Subject: BLA 761142 (Uplizna, inebilizumab-cdon, MEDI-551)

BLA 761142 was submitted on June 11, 2019, by Viela Bio to support marketing authorization of inebilizumab for the treatment of adults with neuromyelitis optica spectrum disorder. Clinical development for the proposed indication was conducted under IND 117295 (Viela Bio). Inebilizumab is also being developed for other indications and many of the nonclinical studies were reviewed under those INDs.

Inebilizumab, a humanized IgGκ monoclonal antibody "directed against the B cell-specific surface antigen CD19," results in depletion of B cells. The nonclinical studies conducted for inebilizumab include pharmacology, PK/ADME, toxicology (≤6 months' duration), and reproductive and developmental toxicology (combined fertility/embryofetal development and pre- and postnatal development) studies. The pivotal nonclinical studies were conducted in a transgenic mouse (hCD19Tg) model that expresses human CD19 because inebilizumab is not pharmacologically active in rodent (mouse, rat) or nonrodent (rabbit, monkey). Carcinogenicity studies were not required, as agreed to by the Division (IND 117295, May 4, 2016).

These studies have been reviewed by Dr. Wilcox (Pharmacology/Toxicology BLA Review and Evaluation, BLA 761142, Barbara J. Wilcox, Ph.D., April 28, 2020). Based on that review (and the previous IND reviews), Dr. Wilcox has concluded the nonclinical data support approval of the BLA for the proposed indication. I concur with that conclusion. Labeling recommendations have been provided separately.

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/

LOIS M FREED
06/01/2020 01:40:59 PM

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

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761142
Supporting document:	SDN1
Applicant's letter date:	6/10/2019
CDER stamp date:	6/11/2019
Product:	Inebilizumab (UPLIZNA)
Indication:	Neuromyelitis optica spectrum disorder (NMOSD)
Applicant:	Viela Bio
Review Division:	Division of Neurology 2
Reviewer:	Barbara J. Wilcox, PhD
Supervisor:	Lois M. Freed, PhD
Division Director (Acting):	Nick Kozauer, MD
Project Manager:	Sandra Folkendt

Disclaimer:

All tables and figures in this review are from the Sponsor unless otherwise designated.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Inebilizumab is a humanized, IgG1 kappa (IgG1κ) monoclonal antibody (mAb) designed to bind the B cell-specific surface antigen CD19 in humans and was developed for treatment of NMOSD. CD19 is expressed on a spectrum of B lymphocytes from pro-B cells to plasmablasts and is also present on some plasma cells. Binding of inebilizumab to human CD19 results in depletion of B lymphocyte populations that express CD19.

1.2 Brief Discussion of Nonclinical Findings

Pharmacology/Mechanism of action

A battery of pharmacology studies was conducted to characterize the specificity, affinity, and mechanism of action of inebilizumab. The data confirm that this product binds to huCD19 with high affinity and specificity and does not bind to CD19 of other species. Therefore, toxicology studies were conducted using a transgenic mouse model expressing human CD19 (huCD19 Tg).

In vitro studies demonstrated that inebilizumab binding results in rapid depletion of B lymphocyte populations through the processes of antibody-dependent cellular cytotoxicity (ADCC) and, to a lesser degree, antibody-dependent cellular phagocytosis (ADCP). The depletion is dose-related in magnitude and duration and does not significantly affect other immune cell populations.

Toxicology

General toxicity studies of 4 weeks, 3 months, and 6 months' duration were conducted using the huCD19Tg mouse model. In general, the observed effects were consistent with the pharmacological activity of inebilizumab. In all studies, dose-related depletion of CD19-expressing B lymphocytes in peripheral blood, bone marrow, and lymphoid tissues (spleen and lymph nodes) was observed. Duration of the effect was dose-dependent, but full recovery was documented if sufficient recovery time was provided. At the HD of 30 mg/kg, full recovery required up to 36 weeks. Skin lesions were observed in the 3-month and 6-month studies that were dose-related in incidence and considered due to immunosuppression.

Reproductive and developmental toxicology

Dose-related effects were observed in a combined fertility and early embryofetal development study conducted in the huCD19Tg mouse. Animals that received IV doses (0, 3, or 30 mg/kg) inebilizumab weekly beginning 15 days prior to mating and through GD15 showed reduced fertility index at both dose levels. The data indicate that the reduced number of pregnancies in mice that had successfully mated was most likely due to early preimplantation loss. No adverse effects were observed on embryofetal development.

Dose-related effects were also observed in a pre-and postnatal development study in which pregnant mice received IV doses of inebilizumab every 3 days from GD6 through weaning of the F1 pups. F1 pups from the LD and HD groups showed near

total absence of B cells. At the end of the study (PND357), B cell levels in F1 pups from the LD and HD groups were similar to control. However, in functional immune testing (TDAR), the pups from both groups showed impaired response to immunization. These data indicate that, although at normal levels, B cells did not function normally.

The neurobehavioral testing conducted as part of the pre- and postnatal development study was not considered adequate for the following 2 reasons: 1) Insufficient number of animals per group was tested, 2) the learning and memory assessment with the Biel maze was not conducted appropriately. In addition to inadequate number of animals, the test utilized only a single path instead of the typical use of 2 paths. However, in spite of the inadequate number of animals evaluated, the male animals from the HD group showed increased peak response in the auditory startle testing for sensory integration. These concerns can be managed with labeling.

1.3 Recommendations

The nonclinical data are adequate to support approval for the intended use.

1.3.3 Labeling

Risk Summary

(b) (4)

Data

Animal Data

(b) (4)

(b) (4)

12.1 Mechanism of Action

(b) (4)

The precise mechanism by which UPLIZNA exerts its therapeutic effects in NMOSD is unknown but is presumed to involve (b) (4)

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies in animals have been performed to determine carcinogenic or mutagenic potential of UPLIZNA.

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 1299440-37-1

USAN Name: Inebilizumab

Code Name: MEDI-551, 16C4, 16C4-aFuc

Molecular Weight: 149 kDa

Structure or Biochemical Description: Humanized IgG1 k monoclonal antibody

Pharmacologic Class: Monoclonal antibody

2.2 Relevant INDs, NDAs, BLAs, and DMFs

IND 117295 (DNP, treatment of neuromyelitis optica spectrum disorders)
IND [redacted] (b) (4)
IND
IND

2.3 Drug Formulation

Table 1 Composition of Drug Product (100 mg/vial)

Ingredient	Unit Formula [a]	Purpose	Quality Standard	Concentration
Active Ingredient				
Inebilizumab	100 mg	Active	In-house Reference Standard	10 mg/mL
Excipients				
L-Histidine	14 mg	[redacted] (b) (4)	USP, Ph. Eur., JP	9 mM
L-Histidine hydrochloride monohydrate	23 mg		Ph. Eur., JP	11 mM
Sodium chloride	41 mg		USP, Ph. Eur., JP	70 mM
Trehalose dihydrate	401 mg		NF, Ph. Eur., JP	106 mM
Polysorbate 80	1 mg		NF, Ph. Eur., JP	0.01% (w/v)
Water for Injection (WFI)	[redacted] (b) (4)		USP, Ph. Eur., JP	[redacted] (b) (4)

JP = Japanese Pharmacopeia; NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

[a] Unit formula is based on the label claim volume of 10 mL.

2.6 Proposed Clinical Population and Dosing Regimen

This product is intended to treat adult patients with neuromyelitis optica spectrum disorders (NMOSD).
The proposed dosing regimen is IV infusion of 300 mg on treatment days 1 and 15, followed by 300 mg every 6 months.

2.7 Regulatory Background

Inebilizumab is being developed for NMOSD under IND 117295. The IND was submitted on January 31, 2014, and was allowed to proceed on February 27, 2014.

3. Studies Submitted

General toxicology, pharmacology, pharmacokinetics, and tissue cross reactivity studies submitted to BLA 761142 were previously reviewed under INDs (b) (4)

Study Number	Reviewer Name (s)	Date(s) of Review(s)	IND Number(s)	Duration and Route
ONC-551-0013	Dr. Mary Jane Hinrichs	5/21/2009	(b) (4)	Acute, IV
ONC-551-0014	Dr. Mary Jane Hinrichs	5/21/2009		Acute, IV
08-2083	Dr. Gary Bond	10/29/2009		1-month, IV
08-2084	Dr. Gary Bond	10/29/2009		3-month, IV
08-2087	Dr. Gary Bond	10/29/2009		1-month in rat
10-2237	Dr. Jane Sohn Dr. Barbara Wilcox Dr. Jane Sohn	3/11/2013 4/11/2013 1/15/2016		3-month, IV-SC Interim report Final report
09-2153	Dr. Jane Sohn	1/15/2016		6-month
MI-0007 ONC-0012	Dr. Mary Jane Hinrichs	5/21/2009		Tissue cross reactivity

Pharmacology studies were reviewed by Drs. Gary Bond (IND (b) (4) 10/29/2009) and Mary Jane Hinrichs (IND (b) (4) 5/21/2009).

The following studies not previously reviewed were also submitted to BLA 761142:

Study # AAO00141
Title: Combined intravenous male and female fertility and embryofetal developmental study of MEDI-551 in huCD19 transgenic mice

Study # (b) (4) -62509
Title: An intravenous study of the effects of MEDI-551 on pre- and postnatal development, including maternal function in mice

3.3 Previous Reviews Referenced

See table, above.

4 Pharmacology

4.1 Primary Pharmacology

Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1 kappa (IgG1κ) monoclonal antibody (mAb) designed to bind the B cell-specific surface antigen CD19 in humans was developed for treatment of NMOSD. CD19 is expressed on a spectrum of B lymphocytes from pro-B cells to plasmablasts and is also present on some plasma cells. Binding of inebilizumab to human CD19 results in specific depletion of B lymphocyte populations.

A series of pharmacology studies was conducted to characterize the binding of inebilizumab, with respect to specificity and affinity for the target, and to define the mechanism of action. Inebilizumab binds specifically to human CD19 and shows no cross-reactivity for CD19 in nonhuman primate, rodents, or rabbits. Therefore, the species selected for nonclinical testing was the human CD19 transgenic mouse model (huCD19 Tg), which was considered the only relevant species. Characterization of the huCD19 Tg mouse model was accepted as a relevant model for testing of inebilizumab (IND (b) (4), Dr. Gary Bond review dated 11/13/2008).

In vivo studies in the huCD19 Tg mouse model and models of autoimmune disease (EAE in huCD19 Tg mice and Sle1-huCD19 Tg mice) demonstrated that inebilizumab specifically depleted B cells in blood and lymphoid tissues without significantly affecting other immune cell populations. Reductions in serum immunoglobulin levels was also demonstrated after B cell depletion in the models of autoimmune disease.

The duration of the inebilizumab-induced B cell depletion was investigated after a single dose of inebilizumab in huCD19 Tg mice. Results demonstrated that the duration of B cell depletion was dose-dependent. Depletion persisted for more than 10 weeks after a single dose of 250 µg . Fourteen to 16 weeks of recovery was required for B cell levels to be restored to control levels. Other immune cell populations (NK, CD3+T cells, neutrophils, monocytes, and dendritic cells) were not significantly affected. Specificity of inebilizumab for B lymphocytes is also supported by in vitro data demonstrating depletion of B cells from human PBMC samples from normal human donors, as well as samples from patients with lymphoblastic leukemia.

In vitro assays were conducted to investigate the mechanism underlying the B cell depletion observed with inebilizumab. The results demonstrated that the B-cell depletion is via ADCC and ADCP. Inebilizumab does not mediate complement dependent cytotoxicity. Early studies investigating the affinities of inebilizumab and other antibody candidates showed that afucosylation resulted in increased affinity for activating Fcγ receptor IIIA and significantly increased B cell depletion through ADCC compared to the fucosylated form.

4.2 Tissue Cross-reactivity

Tissues from human, huCD19 Tg mouse, and Fisher rat were evaluated using standard immunohistochemical methods. In human tissues, specific binding was

observed in spleen, lymph nodes, tonsils, thymus, and gastrointestinal tract. A similar binding pattern was observed in tissues from the huCD19 Tg mouse. Although some specific binding was identified in rat tissues, it was determined to be cytoplasmic and not toxicologically relevant. In addition, pharmacology data indicate the MEDI-551 does not bind to rat CD19. Therefore, the binding in rat tissues was not considered relevant. (Because binding was observed in male rat reproductive tissues, a 1-month toxicology study was conducted to assess potential toxicity in male Fischer 344 rats; no toxicity was observed. This study is not considered relevant and was not reviewed in detail here.)

4.3 Safety Pharmacology

Stand-alone safety pharmacology studies were not conducted for inebilizumab. Safety pharmacology endpoints were evaluated as part of the repeat-dose general toxicology studies.

5 Pharmacokinetics/ADME/Toxicokinetics

Toxicokinetic analysis was included with each general toxicology study. Summary tables are below.

Human PK:

Protocol No.	Study Objective(s)	Study Design	No. of Subjects;	Treatment Details (Drug/Dose/ Form/Route/ Frequency/Duration)	Summary Statistics [a]					Study Report Location
					C_{max} (µg/mL)	T_{max} (d)	AUC_{inf} (µg·d/mL)	$t_{½}$ (d)	V_{ss} (mL) [b]	
Study 1155	To characterize the PK profile of inebilizumab in NMOSD subjects	R, DB, PLC	174	300 mg IV Inebilizumab on Day 1 and Day 15	[116] 108 (45.4%) [c]	0.07 (0.07-14.00) [c]	[3130] 2980 (34.3%)	[18.8] 18.0 (27.2%)	[4380] 4210 (27.3%)	CD-IA-MEDI-551-1155 Module 5.3.5.1

AQP4-IgG = aquaporin-4 autoantibodies; AUC_{inf} = area under the plasma concentration-time curve from Time 0 to infinity; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; DB = double blind; DR = dose rising; IV = intravenous; NA = not applicable; PLC = placebo; R = randomized; SC = subcutaneous; SD = standard deviation; $t_{½}$ = terminal elimination half-life; T_{max} = time to maximum concentration; V_{ss} = volume of distribution.

All PK parameters are rounded to 3 significant figures except T_{max} (rounded to 2 decimal places)

a Parameters are summarized as arithmetic mean (CV%) for CP200 and Study 1102 apart from T_{max} displayed as median (range: min – max). Parameters for Study 1155 are summarized as [arithmetic mean] geometric mean (geometric CV%) apart from T_{max}, displayed as median (range: min – max).

b V_{ss} unit is mL/kg for CP200 and mL for Study 1155.

c Value is calculated from Dose 2 inebilizumab on Day 15 of AQP4-IgG Combined.

Table 3 Summary Statistics of Inebilizumab PK Parameters by Dose Group (Study 1102)

PK Parameter	IV Cohorts			SC Cohorts	
	30 mg (N = 5)	100 mg (N = 4 [b])	600 mg (N = 6)	60 mg (N = 3)	300 mg (N = 3)
T_{max} (d)	0.14 (0.11 – 0.19)	0.07 (0.01 – 0.11)	0.12 (0.11 – 0.18)	2.98 (2.87 – 6.97)	7.92 (7.82 – 8.02)
C_{max} (µg/mL)	17.9 ± 13.2 (73.8%)	43.1 ± 11.4 (26.4%)	248 ± 66.8 (26.9%)	6.67 ± 2.88 (43.2%)	24.7 ± 9.37 (38.0%)
AUC_{last} (µg·d/mL)	436 (NA) [a]	1140 ± 278 (24.4%)	6850 ± 1340 (19.6%)	197 ± 92.6 (46.9%)	788 ± 455 (57.7%)
AUC_{inf} (µg·d/mL)	440 (NA) [a]	1150 ± 286 (24.9%)	6950 ± 1430 (20.6%)	201 ± 91.5 (45.6%)	794 ± 453 (57.1%)
AUC_{inf}/Dose (µg·d/mL/mg)	7.34 (NA) [a]	5.75 ± 1.43 (24.9%)	5.79 ± 1.19 (20.6%)	3.35 ± 1.52 (45.6%)	2.65 ± 1.51 (57.1%)
CL or CL/F (mL/d)	139 (NA) [a]	181 ± 44.5 (24.6%)	180 ± 41.5 (23.4%)	351 ± 177 (50.5%)	457 ± 214 (46.8%)
$t_{½}$ (d)	17.7 (NA) [a]	17.7 ± 6.27 (35.4%)	18.7 ± 2.03 (10.8%)	12.3 ± 1.71 (13.9%)	15.1 ± 4.31 (28.5%)

AUC_{inf} = area under the concentration-time curve from dosing extrapolated to infinity; AUC_{last} = area under the concentration-time curve from dosing to last measurable timepoint; C_{max} = maximum observed concentration; CL = systemic clearance, CL/F = apparent clearance after extravascular administration; IV = intravenous; MEDI-551 = inebilizumab; N = sample size per cohort; NA = not applicable; PK = pharmacokinetic; SC = subcutaneous; $t_{½}$ = terminal elimination half-life; T_{max} = time to maximum concentration.
Parameters are presented as arithmetic mean ± standard deviation (CV%) apart from T_{max}, displayed as median (range: min - max).All PK parameters are rounded to 3 significant figures except T_{max} (rounded to 2 decimal places).
a Standard deviation was not calculated due to limited sample size (n= 2). 2/5 subjects received only one dose and 1 subject had insufficient data.
b Parameters presented were determined based on sample size of 3 as Subject (b) (6) received 130 mg dose; all data from this subject were excluded from summary statistics.
Source: Table 11.4.4.1-1, 1102 CSR.

Pharmacokinetics in huCD19Tg mouse: (TK from 6-month mouse study)

Table 7 Summary Statistics of Toxicokinetic Results for Human CD19 Transgenic Mice (Study 09-2153)

Group	Dose (mg/kg)	Animal gender	Dose #	T_{max} (TK day)	C_{max} (µg/mL)	AUC_{0-7d} (day·µg/mL)	CL (mL/day/kg)	$t_{1/2}$ (Day)	AR	AUC_{0-7d}/Dose (day·µg·kg/mL/mg)
4	3	Female	1	0.04	41.0	141	4.04	7.74	5.27	47.0
			26	175.33	138	743				248
		Male	1	0.04	56.7	166	2.59	19.4	6.99	55.3
			26	175.17	229	1160				387
5	30	Female	1	0.04	529	1610	4.73	12.0	3.94	53.7
			26	175.04	1170	6340				211
		Male	1	0.04	654	1820	3.37	21.3	4.90	60.7
			26	175.17	2020	8910				297

AR = accumulation ratio; AUC_{0-7d} = area under the concentration-time curve from 0 to 7 days postdose; CL = clearance after intravenous administration; C_{max} = Maximum observed concentration; LLOQ = lower limit of quantitation; NA = not applicable; $t_{1/2}$ = elimination half-life; TK = toxicokinetics; T_{max} = Time to the maximum concentration.

TK Parameters were rounded to 3 significant figures after calculations were performed, except for T_{max}.

Accumulation ratios (AR) were determined using $AUC_{0-7d, Dose\ 26}/AUC_{0-7d, Dose\ 1}$

Clearance was calculated as $Dose/AUC_{0-7d, Dose26}$

Samples without a reportable results or with concentrations below LLOQ were excluded from the TK analysis

6 General Toxicology

6.1 Single-Dose Toxicity

In study #ONC551-0013, huCD19 Tg mice (5/sex/group) received single IV injections of inebilizumab at dose levels of 0, 2.5, 10, or 40 mg/kg on study day 1 (SD1). Main study animals were euthanized on SD8, and an additional 5 animals/sex/group were euthanized at the end of recovery on SD29.

The only findings reported for this acute, pilot study were the expected results of the pharmacological activity of Inebilizumab (B cell depletion). Findings included dose-related reductions in B cell populations of splenic white pulp, increased prominence of paracortical T cell zones in lymph nodes, and hyperplasia in the red pulp of the spleen. Similar results were observed in study #ONC551-0014, in which huCD19 Tg mice (5/sex/group) received IV injections of inebilizumab at dose levels of 0, 0.5, 10, or 50 mg/kg on SD1. Results of this study were similar to those of the previous study demonstrating dose-related reductions in B lymphocytes in peripheral blood as well as spleen, thymus, and lymph nodes. At the end of the recovery period, the B cell depletion persisted at the MD and HD in spleen and lymph nodes. Immunophenotyping of peripheral blood and bone marrow showed dose-related B cell depletion, with the greatest effect on pre-B cells, immature, and mature B cells. Little effect was observed on pro-B cells.

6.2 Repeat-Dose Toxicity

Study # 08-2083

Title: A 1-month repeat dose IV toxicity study of MEDI-551 in huCD19 transgenic mice

HuCD19 Tg mice received IV injections of inebilizumab weekly for one month (total of 5 doses) at doses of 0, 0.675, 3.71, or 36.6 mg/kg followed by a 35-week recovery period for females and 37-weeks for males. Test article-related effects were limited to expected results of the pharmacological activity of Inebilizumab: reductions in absolute lymphocyte counts associated with severe reduction in B lymphocytes at all doses at the end of the dosing period. The magnitude of B cell reduction was similar between males and females at the MD and HD but was slightly less severe in LD females relative to LD males. Full recovery (defined as greater than 25% of control) was reached in LD females by 5 weeks after the final dose. LD males did not show recovery until week 16. Females in the MD and HD groups recovered by 20 and 32 weeks, respectively, but males in the MD and HD groups did not show recovery of B cell levels until 28 and 36 weeks, respectively, after the final dose. No effects on peripheral blood NK or T lymphocytes were observed.

B lymphocyte depletion was also detected by tissue FACS analysis in spleen and bone marrow at all doses.

Microscopic examination showed the expected depletion of B-cell regions in the spleen and lymph nodes of all animals at all doses of inebilizumab. Microscopic findings associated with B-cell depletion were not observed at the end of the recovery period.

Study #08-2084

Title: A 3-month repeat-dose intravenous toxicity, toxicokinetics, and immunogenicity study of MEDI-551 in huCD19 transgenic mice

Human CD19 transgenic mice received weekly IV injections of inebilizumab at doses of 0, 0.5, 3, or 30 mg/kg for 13 weeks. Dose-related reductions of peripheral blood B lymphocytes were observed at all dose levels, relative to control, graded severe for the MD and HD groups. Males appeared to show a slightly greater response (range of 1.9 to 3.5% of control) than females (range 2.0 to 5.8% of control) at the end of the dosing period. Tissue immunophenotyping also showed the expected reduction of B lymphocytes in spleen and bone marrow at all dose levels (considered to be 100% depletion at the MD and HD). At the end of the recovery period, B-cell levels were considered fully recovered in spleen and bone marrow. Peripheral blood B-cell levels were considered recovered in the LD group by 12 and 20 weeks after the final dose for females and males, respectively. Females in MD and HD groups were considered recovered by 20 and 28 weeks, respectively; males in the MD and HD groups recovered by 28 and 36 weeks, respectively

Reduction of B cells was evident in microscopic findings of reduced cellularity of the white pulp B-cell regions in spleen and reduced cellularity of B-cell follicles in the cortex of mesenteric and mediastinal lymph nodes. Incidence and severity were dose-related. Complete resolution of these microscopic findings was observed at the end of the recovery period.

Study #10-2237

Title: A 3-month subcutaneous repeat-dose toxicity, toxicokinetics, and immunogenicity study of MEDI-551 in huCD19 transgenic mice (GLP)

In this study, mice (10/sex/group in the main study, 14/sex/group in the 45-week recovery group) received doses of inebilizumab at 0, 3, or 30 mg/kg/week SC or 30 mg/kg/week IV for 13 total doses. Five control animals were euthanized early or were found dead during the study. Of the early decedents that received inebilizumab, 8 were considered related to the test article (4 LD, 3 HDSC, and 1 HDIV); the reason for early euthanasia and morbidity in these animals was extensive skin lesions. One HDIV female was also euthanized early but no cause of death was identified; however, because this was a HD animal, a relationship to the test article cannot be ruled out. A dose-related increase in alopecia was reported, mainly in females. The sponsor indicates that alopecia occurs with relatively high incidence in this strain of mouse.

Although not clearly dose-dependent, an increased incidence of skin ulcerations was observed in survivors that received inebilizumab. The skin lesions were not observed at the end of the recovery period. This finding was considered related to the immunosuppression resulting from B-cell depletion induced by inebilizumab.

Clinical pathology findings demonstrated a dose-related decrease in total lymphocytes and increased absolute eosinophils in males and females in all dose groups. At the end of the 45-week recovery period, lymphocyte levels appeared to be restored but the eosinophil levels did not. Dose-related decreases in globulin levels were observed in both males and females in all dose groups accompanied by increased A/G ratio, findings which persisted through the end of the recovery period.

Target organs identified by microscopic examination were spleen and lymph nodes, and findings were similar to those observed in other toxicity studies (B-cell depletion in splenic white pulp and marked to severe decreased lymph node follicle number and cellularity). At the end of the recovery period, these findings were nearly fully recovered.

Bronchio-alveolar adenomas were observed in 50% (7 of 14) of males in the HDIV group, in recovery animals. Because the findings were apparently dose-related, they were considered related to inebilizumab. However, bronchio-alveolar adenomas were not observed in a 6-month IV study at similar dose levels (see below). For this reason, the lung findings were not considered relevant.

Study #09-2153 Title: A 6-month repeat-dose intravenous toxicity, toxicokinetics, and immunogenicity study of MEDI-551 in huCD10 transgenic mice

Inebilizumab was administered to huCD19Tg mice (24/sex/group) by IV injection weekly for 26 weeks at dose levels of 0, 3, or 30 mg/kg. (Satellite groups of 18/sex were dosed at 3 and 30 mg/kg for TK and immunogenicity and as potential replacement animals.) The dosing period was followed by a 36-week recovery period. No test article-related unscheduled deaths occurred during the dosing period of this study. Two LD animals were euthanized during the recovery period due to skin lesions/ulcerations. This finding is similar to skin lesions observed in the 3-month study. Although not considered a direct effect of the test article, increased vulnerability to infection would be expected in the absence of B cells, which is the direct effect of inebilizumab.

No clear test article-related effects on clinical observations were reported. Isolated observations of skin ulceration of the head and neck were reported for animals from the LD and HD groups during the course of the study. In general, test article-related effects were the expected result of the known pharmacological activity of inebilizumab. Near total depletion of peripheral blood B lymphocytes was observed in both the LD and HD groups during the dosing period as determined by immunophenotyping with FACS analysis. By the end of the 36-week recovery period B cell levels in the LD group were similar to control, but B-cell levels for the HD group were not fully recovered to control levels. B-lymphocyte depletion was also observed in spleen and bone marrow, using tissue immunophenotyping methods, at the end of the dosing period at both dose levels. Using these methods, nearly full recovery was observed at the end of the recovery period. No significant effect on NK cell levels related to inebilizumab was observed. However, increases in neutrophils and monocytes were observed in both dose groups at the end of the dosing period, which normalized by the end of the recovery period. Dose-dependent increases in eosinophils in females of both dose groups were observed at the end of the dosing period (LD: 63%, HD: 138%) followed by partial recovery by the end of the recovery period.

Target organs were spleen, lymph nodes, and bone marrow, with microscopic findings indicative of B cell depletion observed in all animals at both doses: reduced splenic white pulp, reduced B cell zones, reduced number and cellularity of lymphoid follicles in lymph nodes, reduced bone marrow cellularity. Findings in spleen and lymph nodes were considered partially recovered at the end of the recovery period.

7 Genetic Toxicology

Not applicable.

8 Carcinogenicity

Not applicable.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Combined intravenous male and female fertility and embryofetal developmental study of MED-551 in huCD19 transgenic mice

Study no.:	AAO00141
Testing Facility and location:	(b) (4)
Date of study initiation:	March 3, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #:	MEDI-551, NDL4517.072

Methods

Doses:	0, 3, or 30 mg/kg
Frequency of dosing:	Once per week
Dose volume:	5 mL/kg
Route of administration:	IV
Formulation/Vehicle:	10mM Histidine, 75 mM NaCl, 4% Trehalose, 0.02% polysorbate 80, pH 6.0,
Species/Strain:	Mouse, huCD19 Tg, 65 days old at arrival
Number/Sex/Group:	25/sex/group
Study design:	Males received doses every 7 days beginning 28 days prior to cohabitation and through cohabitation to the day before euthanasia. Females received weekly doses beginning 15 days prior to cohabitation and through day 15 of presumed gestation.

Dosage Group	Dosage (mg/kg/dose)	Nominal Concentration (mg/mL)	Dosage Volume (mL/kg)	Number of Mice		Assigned Mouse Numbers	
				Male	Female	Male Mice	Female Mice
I	0 (Vehicle)	0	5	25	25	4701 – 4725	4801 – 4825
II	3 (MEDI-551)	0.6	5	25	25	4726 – 4750	4826 – 4850
III	30 (MEDI-551)	6	5	25	25	4751 – 4775	4851 – 4875

The test article was considered 100% active/pure for the purpose of dosage calculations.
All injections were administered bolus.

Observations and Results

Mortality: (Observations were recorded at least twice daily.)

No unscheduled deaths in F0 females or males related to inebilizumab occurred.

Clinical Signs: (Observations were recorded at least once daily. On dosing days, data were recorded prior to dosing, and within two hours post dose.)

No clinical signs in F0 animals related to the test article were observed.

Body Weight: Body weight was recorded weekly during the dosing period and on the day of euthanasia.

No test article-related effects on body weight or body weight change in F0 animals were observed.

Flow Cytometry: (Blood samples were collected from F0 females on GD15 and from males 3 days prior to euthanasia. At euthanasia of the dams, blood samples from 50% of the fetuses [those designated for soft tissue examination] were collected for B-cell analysis via flow cytometry. Spleens were collected for tissue flow cytometry from 2 male or 2 female fetuses/litter assigned to skeletal evaluation.)

Near complete depletion of total B lymphocytes was observed in peripheral blood from adult males and females at both dose levels. The average B-cell level in control animals was 947 cells/µL compared to averages of 20.3 and 19.1 cells/µL for males in the LD and HD groups, respectively. Results from females were similar in magnitude.

Fetal peripheral blood (pooled by litter) showed low total B-cell levels. B cells expressing human CD19 could not be detected in fetal blood from the LD and HD groups, suggesting fetal exposure to the test article.

Flow cytometry on fetal spleens was not completed due to insufficient cell numbers. In fetal liver, huCD19 was expressed on 60.7% of B lymphocytes from control animals. In treated groups, B lymphocytes expressing huCD19 were observed at 0.32 and 0.15% for the LD and HD groups, respectively.

Estrous cycling: (Evaluated by vaginal cytology for 14 days prior to initiation of dosing and for 14 days after beginning of dosing.)

No effects related to the test article were observed on estrous cycle parameters.

Hematology: (Samples were collected from all F0 females at euthanasia. The parameters listed in the table below were monitored.)

Red blood cell count	White blood cell count
Hemaglobin concentration	Neutrophil count
Hematocrit	Lymphocyte count
Mean corpuscular volume	Monocyte count
Mean corpuscular hemoglobin	Eosinophil count
concentration (MCHC)	Basophil count
Mean corpuscular hemoglobin (MCH)	
Mean platelet volume (MPV)	Large unstained cells
Platelet count	Other cells (as appropriate)

Small elevations in red cell parameters were observed in HD females, accompanied by a small, dose-related (but not statistically significant) increase in reticulocytes.
Small increases in eosinophils were observed in LD and HD females (+83%, relative to control)

Toxicokinetics: (Blood samples were collected from F0 dams on the first and last day of administration and at the time of C-section. Samples were collected from males on the first and last days of dosing. For all animals, samples were collected approximately 2 hours post dose. Samples for TK were collected from fetuses on the day of C-section.)

Detectable levels of inebilizumab were observed in fetal blood, confirming exposure of the fetuses to the test article. Fetal-to-maternal concentration ratios for the LD and HD groups were 114% and 31.1%, respectively.

Dosing Solution Analysis (Samples were collected from each prepared dosing solution on the first and last day of dosing.)

All formulation samples were determined to be within pre-established acceptance criteria for concentration, purity, and stability.

Terminal Procedures:

Males were euthanized on SD61 to 63. Reproductive organs were collected, and sperm analysis was conducted using samples from the left cauda epididymis.

Sperm analysis results:
No test article-related effects on sperm motility, count, or density were observed. The data are summarized in the table below.

TABLE A8 (PAGE 1): SPERM MOTILITY, COUNT AND DENSITY - SUMMARY - MALE MICE

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	3 (MEDI-551)	30 (MEDI-551)
MICE TESTED	N	25	25	24a
LEFT CAUDA EPIDIDYMAL SPERM MOTILITY				
NUMBER MOTILE	MEAN±S.D.	742.5 ± 333.8 [20]b	928.3 ± 418.9 [20]b	1027.3 ± 513.9 [22]b
MOTILE PERCENT	MEAN±S.D.	89.0 ± 7.2 [20]b	91.7 ± 4.0 [20]b	91.4 ± 6.7 [22]b
STATIC COUNT (NONMOTILE)	MEAN±S.D.	75.7 ± 34.9 [20]b	71.8 ± 24.5 [20]b	73.1 ± 18.8 [22]b
TOTAL COUNT c	MEAN±S.D.	818.2 ± 335.6 [20]b	1000.0 ± 430.2 [20]b	1100.4 ± 520.0 [22]b
CAUDA EPIDIDYMAL SPERM COUNT				
SPERM COUNT d	MEAN±S.D.	69.4 ± 22.7	65.2 ± 15.8	63.7 ± 12.8
SPERM DENSITY e	MEAN±S.D.	2607.33 ± 825.03	2432.42 ± 577.60	2361.51 ± 620.27

a. Excludes values for mouse 4769, which was sacrificed on day 57 of study due to adverse clinical observations.
b. Excludes values for mice which had motility data that reflected drifting debris.
c. Sum of number motile and static count. Groups of five fields were evaluated until a sperm count of at least 200 was achieved or 20 fields were evaluated.
d. Sperm count used in the calculation of sperm density. Ten fields were evaluated.
e. The sperm density was calculated by dividing the sperm count by the volume in the image area (38.3×10^{6} mL), multiplying by 2 (dilution factor + 1) and multiplying by 10^{-6} to obtain the sperm concentration. The calculated sperm concentration value (rounded to 1 decimal place) was multiplied by 10 (volume) and divided by the weight of the left cauda epididymis (see Table A13 for the weight of the left cauda epididymis) to obtain the sperm density. The calculated value will vary by approximately 0.8% from the Computer Automated Sperm Analysis because the digital image evaluated is slightly smaller (4 pixels) than the actual field causing a slight underestimate of the actual volume and an overestimate of the concentration.

Necropsy data are summarized below for males:

TABLE A5 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - MALE MICE

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG)a		0 (CONTROL)	3 (MEDI-551)	30 (MEDI-551)
MICE EXAMINED b	N	25	25	25
UNSCHEDULED SACRIFICE	N	0	0	1c
APPEARED NORMAL	N	23	24	24
VENTRAL SURFACE OF NECK: FIRM DARK RED MASS PRESENT SUBCUTANEOUSLY	N	1	0	0
THORACIC REGION AND VENTRAL SURFACE OF NECK: RED GELATINOUS MATERIAL PRESENT SUBCUTANEOUSLY	N	2	0	0
EPIDIDYMIDES: RIGHT, TAN FIRM MASS	N	0	1	0
RIGHT, LARGE CAPUT	N	0	1	0
PROSTATE: CAUDAL REGION, DARK RED AREA	N	0	0	1

a. Dosage occurred once every 7 days.
b. Refer to the individual clinical observations table (Table A9) for external observations confirmed at necropsy.
c. Mouse 4769 was sacrificed on day 57 of study due to adverse clinical observations.

No gross observations related to the test article were reported.

Necropsy, F0 females:
Dams were euthanized on GD18 and gross necropsy was conducted. Uteri were examined for implantation sites. Ovaries were examined for number and distribution of corpora lutea. Fetuses were weighed, examined for sex, and examined for gross lesions. Approximately 50% of fetuses were examined for soft tissue abnormalities and the remaining 50% were examined for skeletal abnormalities.

Fertility Parameters: (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)
Significant reductions of the fertility index were observed for both LD and HD groups There was no dose-related difference in mean number of days in cohabitation or in number of males that mated. Data are summarized in the table below:

TABLE A4 (PAGE 1): MATING AND FERTILITY - SUMMARY - MALE MICE

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG)a		0 (CONTROL)	3 (MEDI-551)	30 (MEDI-551)
MICE IN COHABITATION	N	25	25	25
DAYS IN COHABITATION	MEAN±S.D.	1.9 ± 1.3	2.0 ± 1.2	2.3 ± 2.3 [24]b
MICE THAT MATED	N(%)	25(100.0)	25(100.0)	25(100.0)
FERTILITY INDEX c	N/N (%)	24/ 25 (96.0)	19/ 25* (76.0)	16/ 25** (64.0)
MICE WITH CONFIRMED MATING DATES	N	25	25	25
MATED WITH FEMALE				
DAYS 1-7	N(%)	25(100.0)	25(100.0)	24(96.0)
DAYS 8-14	N(%)	0(0.0)	0(0.0)	1(4.0)
MICE PREGNANT/MICE IN COHABITATION	N/N (%)	24/ 25 (96.0)	19/ 25* (76.0)	16/ 25** (64.0)

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred once every 7 days.
b. Excludes value for mouse 4764; the female was not placed into cohabitation on the third day of cohabitation.
c. Number of pregnancies/number of mice that mated.
* Significantly different from the control group value (p≤0.05).
** Significantly different from the control group value (p≤0.01).

Caesarean and litter parameters:

TABLE B8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - FEMALE MICE

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG)a		0 (CONTROL)	3 (MEDI-551)	30 (MEDI-551)
MICE TESTED	N	25	25	25
PREGNANT	N(%)	24(96.0)	19(76.0)*	16(64.0)**
FOUND DEAD	N(%)	0(0.0)	0(0.0)	1(6.2)
UNSCHEDULED SACRIFICE	N(%)	1(4.2)	0(0.0)	0(0.0)
ABORTED AND SACRIFICED	N(%)	1(4.2)	0(0.0)	0(0.0)
DELIVERED AND SACRIFICED	N(%)	0(0.0)	1(5.3)	1(6.2)
MICE PREGNANT AND CAESAREAN-SECTIONED ON DAY 18 OF GESTATION	N	22	18	14
CORPORA LUTEA	MEAN±S.D.	10.0 ± 1.2	10.0 ± 0.9	9.6 ± 2.3
IMPLANTATIONS	MEAN±S.D.	9.9 ± 1.2	10.0 ± 0.9	9.5 ± 2.4
% PREIMPLANTATION LOSS	MEAN±S.D.	0.4 ± 1.9	0.0 ± 0.0	1.5 ± 4.0
LITTER SIZES	MEAN±S.D.	9.1 ± 1.3	8.6 ± 1.6	8.4 ± 2.5
LIVE FETUSES	N	199	155	117
	MEAN±S.D.	9.0 ± 1.3	8.6 ± 1.6	8.4 ± 2.5
DEAD FETUSES	N	1	0	0
	MEAN±S.D.	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.8 ± 1.0	1.4 ± 1.4	1.1 ± 1.0
EARLY RESORPTIONS	N	15	22	15
	MEAN±S.D.	0.7 ± 0.9	1.2 ± 1.4	1.1 ± 1.1
LATE RESORPTIONS	N	3	4	1
	MEAN±S.D.	0.1 ± 0.4	0.2 ± 0.4	0.1 ± 0.3
% POSTIMPLANTATION LOSS	MEAN±S.D.	8.4 ± 10.0	14.5 ± 14.2	13.3 ± 12.1

% PREIMPLANTATION LOSS = [(NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS) / NUMBER OF CORPORA LUTEA] x 100
% POSTIMPLANTATION LOSS = [(NUMBER OF IMPLANTATIONS - NUMBER OF LIVE FETUSES) / NUMBER OF IMPLANTATIONS] x 100
a. Dosage occurred once every 7 days.
* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

TABLE B8 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - FEMALE MICE

DOSAGE GROUP		I	II	III
DOSAGE (MG/KG)a		0 (CONTROL)	3 (MEDI-551)	30 (MEDI-551)
MICE TESTED	N	25	25	25
PREGNANT	N(%)	24(96.0)	19(76.0)	16(64.0)
FOUND DEAD	N(%)	0(0.0)	0(0.0)	1(6.2)
UNSCHEDULED SACRIFICE	N(%)	1(4.2)	0(0.0)	0(0.0)
ABORTED AND SACRIFICED	N(%)	1(4.2)	0(0.0)	0(0.0)
DELIVERED AND SACRIFICED	N(%)	0(0.0)	1(5.3)	1(6.2)
MICE PREGNANT AND CAESAREAN-SECTIONED ON DAY 18 OF GESTATION	N	22	18	14
DAMS WITH ANY RESORPTIONS	N(%)	11(50.0)	13(72.2)	10(71.4)
DAMS WITH ALL CONCEPTUSES DEAD OR RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE FETUSES	N(%)	22(100.0)	18(100.0)	14(100.0)

a. Dosage occurred once every 7 days.

Offspring (Malformations, Variations, etc.)

No dose-related skeletal or soft tissue malformations or variations were observed.

Immunophenotyping:
Peripheral blood: Severe reduction in total B lymphocytes was observed in peripheral blood of F0 females at both dose levels.
Fetal blood (pooled by litter): B lymphocytes were severely reduced relative to maternal levels in all dose groups, including control. This finding is partially due to the immature state of the fetal immune system. However, B lymphocytes expressing mouse CD19 were detected in fetal blood from all groups at similar levels. B cells expressing huCD19 were detected in control fetal blood (low relative to adult) but not in blood from either the LD or HD groups.

In immunophenotyping of fetal liver tissue, a severe reduction of B cell expressing huCD19 was observed in both LD and HD groups (Control: 60.7%, LD: 0.32%, HD: 0.15%).

Conclusion:
No NOAEL could be determined due to the reduced fertility index at both the LD and HD.

9.2 Prenatal and Postnatal Development

Study title: An intravenous study of the effects of MEDI-551 on pre-and postnatal development, including maternal function in mice

Study no.:	(b) (4)-62509
Testing Facility and location:	(b) (4)
Date of study initiation:	April, 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MEDI-551, BM0001, 99.5%

Methods

Doses:	0, 3, or 30 mg/kg
Frequency of dosing:	F0 dams: test article was administered on GD 6, 9, 12, 15, and 18 and on LD 1, 4, 7, 10, 14, 17, and 20.
Dose volume:	3.0 mL/kg
Route of administration:	IV (bolus)
Formulation/Vehicle:	75mM NaCl, 106 mM trehalose dihydrate, 0.02% polysorbate 80, 10 mM histidine/diluted with 0.9% NaCl
Species/Strain:	Mouse, huCD19 Tg, heterozygous, (C57BL/6J)
Number/Sex/Group:	Timed pregnant females of sufficient number were dosed in order to provide appropriate number (20, 25, or 30/group) of F1 offspring with the specific genotype

Group Number	Test Article	Dosage Level (mg/kg/dose)[a]	Dosage Concentration (mg/mL)	Dosage Volume (mL/kg)	Number of F_0 Females[b]
1	Placebo Control	0	0	3.0	111
2	MEDI-551	3	1.0	3.0	130
3	MEDI-551	30	10	3.0	129

[a] No correction factor was used.
[b] Numbers of F_0 females vary by group depending on the number of pregnant dams needed to produce sufficient offspring for the F_1 generation.

F1 subgroup allocation:

Group Number	Test Article	Subgroup 1[a]		Subgroup 2[a]		Subgroup 3[a]	
		Male	Female	Male	Female	Male	Female
1	Placebo	25	25	20	20	30	30
2	MEDI-551	25	25	20	20	30	30
3	MEDI-551	25	25	20	20	30	30

[a] - No more than 2 pups/sex/litter were assigned to the same subgroup (see Appendix 1 - Study Protocol and Deviations).

Offspring Subgroup Allocation

Maximum No. Selected (Subgroup)	Age	Evaluation
10/sex/group (1)[a]	PND 60	Auditory Startle
10/sex/group (1)[a]	PND 21 and 61	Motor Activity
10/sex/group (1)[a]	PND 62	Learning and Memory
25/sex/group (1)	Minimum of 85 days	Breeding
10/sex/group (2a)	PND 50	Immunophenotyping
10/sex/group (2d)	PND 357	Immunophenotyping
15/sex/group (3a)	PND 357, 364, and 371	Anti-KLH IgM and IgG Evaluation
15/sex/group (3b)	PND 385, 392, and 399	Anti-KLH IgM and IgG Evaluation

[a] The same pups were used for Auditory Startle, Motor Activity, and Learning and Memory

Observations and Results

F0 Dams:

Mortality: (observations were recorded twice daily.)
Unscheduled deaths were observed in the control and HD groups (5 and 7 in control and HD groups, respectively). The number of unscheduled F0 deaths in the HD group was slightly higher than the number of deaths in the control group, but the sponsor considered these deaths to be related to the transgenic strain and not to the test article. No clinical observations were reported preceding these deaths. No test article-related macroscopic observations were reported at necropsy.

Text Table 19
F_0 Unscheduled Deaths

Animal No.	Group (mg/kg/dose)	Day of Death	Type of Death
4310	0	GD09	Euthanized in Extremis
4335	0	GD18	Found Dead
8818	0	LD20	Found Dead
1323	0	GD21	Euthanized in Extremis
1355	0	LD01	Euthanized in Extremis
1331	30	GD09	Euthanized in Extremis
1346	30	GD23	Euthanized in Extremis
1348	30	LD01	Euthanized in Extremis
1366	30	LD02	Euthanized in Extremis
6618	30	LD02	Euthanized in Extremis
6435	30	LD20	Euthanized in Extremis
6452	30	LD02	Euthanized in Extremis

GD = Gestation Day
LD = Lactation Day

Clinical observations: (Observations were recorded once daily.)
No test article-related clinical observations were reported.

Body weight: (Data were recorded on GD3, 6, 9, 12, 15, and 18 and on LD 1, 4, 7, 10, 14, 17, and 21.)
No test article-related effects were observed for F0 dams during gestation or lactation.

Food consumption: (Data were recorded on GD3, 6, 9, 12, 15, and 18 and on LD1, 4, 7, 10, 14, 17 and 21.)
No test article-related effects were observed.

Gestation and parturition:
No test article-related effects were observed on gestation length or the parturition process.

Necropsy: Terminal procedures for F0 dams are summarized in the table below. All animals received complete necropsy examination. Uteri were assessed for implantation sites.

Text Table 11
Terminal Procedures

Group No.	No. of Animals	Scheduled Euthanasia Day	Necropsy Procedures	
			Necropsy	Tissue Collection
1	106	Lactation Day 21[a]	X	X[b]
2	130			
3	122			
Unscheduled Deaths			X	X[b]

X = Procedure conducted
[a] Females that failed to deliver were euthanized on Postmating Day 23 and females with total litter loss were euthanized within 24 hours of litter loss.
[b] Gross lesions and injection sites.

No macroscopic observations were reported for the unscheduled F0 deaths (F0 dams with total litter loss, or that failed to deliver or were euthanized on LD21).

No effects related to the test article were observed on the number of implantation sites or the number of pups born relative to the number of implantation sites.

Toxicokinetics: (Blood samples were collected from 5 dams/group on LD 21 at euthanasia. F1 pup blood samples were collected on PND 21 from 3/sex/ group from a total of 12/sex/group. PND 21 was the only time point for TK analysis. Therefore, no calculation of TK parameters was conducted.

Maternal inebilizumab levels are summarized in the table below:

Text Table 24
F_0 Maternal Serum Concentrations

Dosage Level (mg/kg/dose)	Number of Animals Represented	Mean Time after Final Dose (hours)	Mean MEDI-551 Concentration (µg/mL)
0	20	24.68	<0.02
3	22	25.25	46.70
30	19	25.96	520.95

F1 Generation:
Mortality: (Observations were recorded twice daily.)
No difference among groups was observed in mean number of pups born, live litter size, percentages of males/females/litter, or postnatal survival to PND21.
A higher than expected incidence of total litter loss was observed but was similar among groups (127, 82, 107 in the control, LD, and HD groups, respectively). These unscheduled deaths were considered related to the transgenic strain of mice and not to the test article. No internal observations attributable to the test article were reported in necropsies of F1 pups found dead or euthanized in moribund condition.

Clinical observations: (Clinical observations were recorded on PND 1, 4, 7, 10, 14, 17, and 21.)
No test article-related clinical signs were observed in F1 pups.

The number of missing, assumed cannibalized, F1 pups was similar across groups (21, 34, and 23 in the control, LD, and HD groups, respectively.)
A high incidence of missing digits in the F1 pups, observed across all dose groups including control, was attributed to mechanical injury (tattooing for identification).

Body weight: (F1 pups were weighed on PND1, 4, 7, 10, 14, 17, and 21.)
No significant test article-related effect on F1 pup body weight or body weight change was observed in LD males or females or in HD males. A very small reduction in mean body weight gain was observed in HD females. Mean body weight at the end of the recovery period for HD females was 4.8% lower than control. The magnitude of this reduction is not considered adverse.

Physical development and neurobehavioral evaluation: F1 pups assigned to Subgroup 1 were used for physical development milestones, auditory startle, locomotor activity, and learning and memory evaluation.

Sexual maturation (Balanopreputial separation/vaginal patency):
No effects related to the test article were observed on sexual maturation parameters.

Estrous cycle: (Vaginal swabs were conducted on females for 10 consecutive days prior to cohabitation.)
No significant test article-related effect was observed on estrous cycle length

Neurobehavioral evaluation: (The neurobehavioral testing used 10 pups/sex/group.)

> *Learning and memory*: (Evaluations were conducted using the Biel maze, beginning on PND62, on 10/sex/group.) No adverse effects related to inebilizumab were observed. However, an insufficient number of pups were tested, and the Biel maze test included use of only the A path instead of the typical use of A and B paths). The learning and memory evaluation is not considered adequate.
>
> *Auditory startle response*: (Evaluated in 10 pups/sex/group on PND60.)
> PEAK response values in all HD male animals were significantly higher relative to control. The effect, which became more pronounced over the test session, was considered test article-related. This finding was not observed in females. Because the difference was of low magnitude (C= 1089.6 vs. 18042.4 for HD males, units not specified), the Sponsor does not consider the effect adverse.
>
> *Motor activity*: (Motor activity was evaluated by standard methods using the same animals from Subgroup1 that were used for the auditory startle response testing. Animals were tested on PND21 and 61 with 10 animals/sex/group.)
> No test article-related effects on motor activity were observed.

Mating: Subgroup 1 pups were paired for up to 15 days of cohabitation and assessed for evidence of mating.

No test article-related effects on mating parameters were observed.

Text Table 20
Results of Reproductive Performance

Parameter	Dose Level (mg/kg/dose)		
	0	3	30
Male Mating Index (%)	100.0	100.0	100.0
Female Mating Index (%)	100.0	100.0	100.0
Male Fertility Index (%)	84.2	92.0	100.0
Female Fertility Index (%)	86.4	92.0	96.0
Male Copulation Index (%)	84.2	92.0	100.0
Female Conception Index (%)	86.4	92.0	96.0
Estrous Cycle Length (days)	4.2	4.3	4.4
Pre-Coital Interval (days)	2.2	2.0	2.5

a (b) (4) historical control data
None statistically significantly different from the control group.

Reproductive Function: F1, Subgroup 1 (Subgroup 1 pups were used for both neurobehavioral evaluations and reproductive function.)

Pregnancy and litter parameters are summarized in the tables below. A slightly higher rate of early resorptions, total resorptions, and post-implantation loss was observed in the HD group.

The number of fetuses and litters available for evaluation were 137(18), 169(22), and 164(23) for the control, LD and HD groups, respectively.
No fetal malformations related to inebilizumab were observed.

TABLE 42 (F2 - SUBGROUP 1)
PROJECT (b) (4) IV STUDY OF MEDI-551 ON PRE- AND POSTNATAL DEVELOPMENT IN MICE PAGE 1
SPONSOR: SUMMARY OF FETAL DATA AT SCHEDULED NECROPSY

GROUP	SEX M	SEX F	VIABLE FETUSES	DEAD FETUSES	RESORPTIONS EARLY	RESORPTIONS LATE	POST IMPLANTATION LOSS	IMPLANTATION SITES	CORPORA LUTEA	PRE IMPLANTATION LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES
1 TOTAL	71	66	137	0	15	0	15	152	166	14	NA	18
MEAN	3.9	3.7	7.6	0.0	0.8	0.0	0.8	8.4	9.2	0.8	1.09	
S.D.	1.55	1.68	1.20	0.00	0.92	0.00	0.92	0.70	1.48	1.48	0.052	
2 TOTAL	78	91	169	0	18	0	18	187	197	10	NA	22
MEAN	3.5	4.1	7.7	0.0	0.8	0.0	0.8	8.5	9.0	0.5	1.09	
S.D.	1.65	1.78	1.70	0.00	0.85	0.00	0.85	1.34	1.05	0.80	0.102	
3 TOTAL	77	87	164	0	26	0	26	190	197	7	NA	24
MEAN	3.2	3.6	6.8	0.0	1.1	0.0	1.1	7.9	8.2	0.3	1.09	
S.D.	1.77	1.64	1.99	0.00	1.21	0.00	1.21	1.86	1.89	0.55	0.057	

None significantly different from control group
NA = NOT APPLICABLE
MEAN NUMBER OF VIABLE FETUSES, MEAN NUMBER OF IMPLANTATION SITES, MEAN NUMBER OF CORPORA LUTEA,
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

1- 0 MG/KG/DAY 2- 3 MG/KG/DAY 3- 30 MG/KG/DAY

PLSUv5.12
02/21/2018

TABLE 43 (F2 - SUBGROUP 1)

PROJECT (b) (4)
SPONSOR:

IV STUDY OF MEDI-551 ON PRE- AND POSTNATAL DEVELOPMENT IN MICE
SUMMARY OF FETAL DATA AT SCHEDULED NECROPSY [% PER LITTER]

PA

GROUP:	0 MG/KG/DAY	3 MG/KG/DAY	30 MG/KG/DAY
CORPORA LUTEA			
MEAN	9.2	9.0	8.2
S.D.	1.48	1.05	1.89
N	18	22	24
IMPLANTATION SITES			
MEAN	8.4	8.5	7.9
S.D.	0.70	1.34	1.86
N	18	22	24
VIABLE FETUSES (%)			
MEAN	90.0	89.3	83.5
S.D.	10.97	12.68	22.57
N	18	22	24
DEAD FETUSES (%)			
MEAN	0.0	0.0	0.0
S.D.	0.00	0.00	0.00
N	18	22	24
EARLY RESORPTIONS (%)			
MEAN	10.0	10.7	16.5
S.D.	10.97	12.68	22.57
N	18	22	24

PROPORTIONAL (%) DATA COMPARED USING DUNN'S TEST
CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
MODIFIED STATISTICS USED. * INDICATES PARAMETRIC ANALYSIS AND + INDICATES NON-PARAMETRIC ANALYSIS.
None significantly different from control group

TABLE 43 (F2 - SUBGROUP 1)

PROJECT (b) (4)
SPONSOR:

IV STUDY OF MEDI-551 ON PRE- AND POSTNATAL DEVELOPMENT IN MICE
SUMMARY OF FETAL DATA AT SCHEDULED NECROPSY [% PER LITTER]

PAGE 2

GROUP:	0 MG/KG/DAY	3 MG/KG/DAY	30 MG/KG/DAY
LATE RESORPTIONS (%)			
MEAN	0.0	0.0	0.0
S.D.	0.00	0.00	0.00
N	18	22	24
TOTAL RESORPTIONS (%)			
MEAN	10.0	10.7	16.5
S.D.	10.97	12.68	22.57
N	18	22	24
PRE-IMPLANTATION LOSS (%)			
MEAN	7.0	5.3	3.4
S.D.	11.54	10.33	6.30
N	18	22	24
POST-IMPLANTATION LOSS (%)			
MEAN	10.0	10.7	16.5
S.D.	10.97	12.68	22.57
N	18	22	24
MALES (%)			
MEAN	52.3	47.7	46.0
S.D.	22.14	21.14	21.34
N	18	22	23

PROPORTIONAL (%) DATA COMPARED USING DUNN'S TEST
MODIFIED STATISTICS USED. * INDICATES PARAMETRIC ANALYSIS AND + INDICATES NON-PARAMETRIC ANALYSIS.
None significantly different from control group

Immunotoxicity:

Immunophenotyping: (Subgroup 2 F1 pups, 10/sex/group, were evaluated on PND50 and 357.)
Lymphocyte subsets assessed are listed in the table below.

Text Table 8
Cell Subsets and Phenotypes

Cell Subsets	Phenotype
Total T-Lymphocytes	CD3e+
Total B-Lymphocytes	B220+
B-cell subset	B220+ mCD19+ huCD19+
B-cell subset	B220+ mCD19+
B-cell subset	B220+ huCD19+
Natural Killer Cells	CD3e- NK1.1+

On PND50, total B lymphocytes were depleted by 97% and 100% in the LD and HD groups, respectively, relative to control. No other immune cell subsets were affected. On PND 357, mean absolute counts of all subsets (including B lymphocytes) were similar to control levels.

Text Table 22
Summary of MEDI-551-Related Flow Cytometry Findings
[Percent Difference from Control]

Parameter	Males (F1 generation) (mg/kg/dose)			Females (F1 generation) (mg/kg/dose)		
	0 [a]	3 [a]	30 [a]	0 [a]	3 [a]	30 [a]
Total T-Lymphocytes (CD3e+) (thous/µL)						
PND 50	0.92 [-]	1.18 [28.3]	1.15 [25.0]	1.07 [-]	1.17 [9.3]	1.40 [30.8]
PND 357	0.64 [-]	0.39 [-39.1]	0.56 [-12.5]	0.53 [-]	0.20** [-62.3]	0.43 [-18.9]
Total B-Lymphocytes (B220+) (thous/µL)						
PND 50	0.38 [-]	**0.01**** **[-97.4]**	**0.01**** **[-97.4]**	0.39 [-]	**0.01**** **[-97.4]**	**0.01**** **[-97.4]**
PND 357	0.39 [-]	0.52 [33.3]	0.39 [0.0]	0.27 [-]	0.22 [-18.5]	0.28 [3.7]
B-cell subset 1 (B220+mCD19+) (thous/µL)						
PND 50	0.40 [-]	**0.01**** **[-97.5]**	**0.01**** **[-97.5]**	0.42 [-]	**0.01**** **[-97.6]**	**0.01**** **[-97.6]**
PND 357	0.41 [-]	0.52 [26.8]	0.39 [-4.9]	0.26 [-]	0.21 [-19.2]	0.27 [3.8]
B cells subset 2 (B220+hCD19+) (thous/µL)						
PND 50	0.36 [-]	**0.00**** **[-100.0]**	**0.00**** **[-100.0]**	0.37 [-]	**0.00**** **[-100.0]**	**0.00**** **[-100.0]**
PND 357	0.40 [-]	0.53 [32.5]	0.39 [-2.5]	0.26 [-]	0.23 [-11.5]	0.28 [7.7]
B cells subset 3 (B220+mCD19+hCD19+) (thous/µL)						
PND 50	0.35 [-]	**0.00**** **[-100.0]**	**0.00**** **[-100.0]**	0.36 [-]	**0.00**** **[-100.0]**	**0.00**** **[-100.0]**
PND 357	0.37 [-]	0.49 [32.4]	0.37 [0.0]	0.25 [-]	0.20 [-20.0]	0.26 [4.0]
NK cells (CD3e-NK1.1+) (thous/µL)						
PND 50	0.08 [-]	0.05* [-37.5]	0.05* [-37.5]	0.09 [-]	0.06 [-33.3]	0.08 [-11.1]
PND 357	0.05 [-]	0.10 [100.0]	0.08 [60.0]	0.06 [-]	0.06 [0.0]	0.06 [0.0]

Bold = Values considered to be MEDI-551 related.
[-] = Percent Differences from Control group.
a= Male and Female animals that might have been exposed to 0, 3 or 30 mg/kg/day of MEDI-551 in utero and via maternal milk during lactation.
* = Significantly different from the control group at 0.05 using Dunnett's test.
** = Significantly different from the control group at 0.01 using Dunnett's test.

TDAR:
Subgroup 3 F1 pups were used for functional immune testing by TDAR using standard methods. KLH was administered on PND357 and PND385. Each KLH administration

used separate groups of pups (5/sex/group). Blood samples were collected 7 and 14 days after each KLH administration.

After the each KLH immunizations, markedly lower levels of anti-KLH IgM and IgG responses were observed in both males and females in LD and HD groups.
The data are summarized in the following table.

Text Table 23
Summary of MEDI-551-Related Primary and Secondary IgG and IgM KLH ELISA Findings
[Percent Difference from Control]

Parameter	Males (mg/kg/dose)			Females (mg/kg/dose)		
	0 [a]	3 [a]	30 [a]	0 [a]	3 [a]	30 [a]
Primary IgG KLH (ug/mL)						
PND 357	< LLQ	< LLQ	< LLQ	0.18	< LLQ	< LLQ
PND 364	6.33	**< LLQ**	**4.12 [-34.9]**	5.08	**< LLQ**	**7.48 [47.2]**
PND 371	18.04	**2.46 [-86.4]**	**0.82 [-95.5]**	27.97 [-]	22.68 [-18.9]	**3.88 [-86.1]**
Primary IgM KLH (ug/mL)						
PND 357	0.92	< LLQ	1.19 [29.3]	0.45 [-]	0.70 [55.6]	0.51 [13.3]
PND 364	1.49	0.60 [-59.7]	**0.98 [-34.2]**	1.44	0.95 [-34.0]	**0.60* [-58.3]**
PND 371	1.39	0.99 [-28.8]	**< LLQ**	1.09	2.18 [100.0]	**< LLQ**
Secondary IgG KLH (ug/mL)						
PND 385	182.03 [-]	**13.86 [-92.4]**	**20.51 [-88.7]**	169.42	241.97 [42.8]	**< LLQ**
PND 392	14233.72	**1413.58 [-90.1]**	**52.14 [-99.6]**	719.75	4401.80 [511.6]	**47.09 [-93.5]**
PND 399	681.45	**10.31 [-98.5]**	**37.39 [-94.5]**	3880.92	**118.23 [-97.0]**	**28.76 [-99.3]**
Secondary IgM KLH (ug/mL)						
PND 385	1.04 [-]	0.66 [-36.5]	0.62 [-40.4]	0.75	3.28 [337.3]	0.53 [-29.3]
PND 392	10.86	4.39 [-59.6]	**2.32* [-78.6]**	1.73	3.93 [127.2]	**2.12 [22.5]**
PND 399	0.98	2.06 [110.2]	1.00 [2.0]	7.60	**0.63 [-91.7]**	**1.10** [-85.5]**

Bold = Values considered to be MEDI-551-related.
[-] = Percent Differences from Control group.
a= Male and Female offspring exposed to 0, 3 or 30 mg/kg/day of MEDI-551 in utero and via maternal milk during lactation.
* Significantly different from the control group at 0.05 using Dunnett's test.
** Significantly different from the control group at 0.01 using Dunnett's test.
LLQ = Lower limit of Quantitation

These data indicate that, although the B-cell levels on PND357 were normal, the function of these cells was impaired.

F1 terminal procedures:

Text Table 12
Terminal Procedures

Group No.	No. of Animals	Scheduled Euthanasia Day	Necropsy Procedures	
			Necropsy	Tissue Collection
1	120	PND 21	X	X[a]
2	115			
3	105			
Unscheduled Deaths			X	X[a]

X = Procedure conducted
[a] Gross lesions only.

Terminal procedures for the selected F1 pups are summarized in the table below. Subgroup 3 F1 pups were not necropsied.

Text Table 13
Terminal Procedures

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	25	22	Males PND 106–129	X	X	-	Select Tissues[a]	Select Tissues[a]
2	25	25	Females Gestation Day 18[b]				Select Tissues[a]	Select Tissues[a]
3	24	25					Select Tissues[a]	Select Tissues[a]
1	20	19	Males PND 50 or 357	X	X	-	Select Tissues[a]	Select Tissues[a]
2	20	20	Females PND 50 or 357				Select Tissues[a]	Select Tissues[a]
3	19	20					Select Tissues[a]	Select Tissues[a]
1	30	27	Males PND 357–399	-	-	-	Select Tissues[a]	-
2	25	35	Females PND 357–399				Select Tissues[a]	-
3	29	29					Select Tissues[a]	-
Unscheduled Deaths				X	X	-	Select Tissues[a]	Select Tissues[a]

X = Procedure conducted; - = not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues
[b] Females with evidence of abortion or premature delivery were euthanized on the day of abortion or delivery.

Tissue collection from pups in the selected Subgroups 1 and 2 is summarized in the tables below.

Text Table 14
Tissue Collection and Preservation - Subgroup 1

Ovaries (2) Uterus[a]	Testis with epididymis and vas deferens (2)[b] All gross (internal) lesions (when possible)[c] Tail tip[d]

Text Table 15
Tissue Collection and Preservation - Subgroup 2

Bone with Marrow Sternebrae Femur Lymph Nodes Axillary (2) Mandibular (2) Mesenteric	Spleen Thymus All gross lesions (when possible)[a] Tail tip[b]

Tail tips were collected from Subgroup 3 pups for possible future genotyping.

Macroscopic examination (F1)

No test article-related macroscopic observations were reported for Subgroup1 and Subgroup 2a males and females and Subgroup 2d males. In subgroup 2d females, macroscopic observations associated with lymphoma were observed in 2 LD females and 1 HD female. The relationship of the test article is uncertain but cannot be ruled out.

Histopathology (F1)

At the PND50 necropsy, microscopic findings related to the test article were observed in lymphoid tissues (spleen, lymph nodes) in all LD and HD animals examined. The findings are expected results of the pharmacological activity of inebilizumab (B-lymphocyte depletion). Microscopic findings are summarized below:

At the PND357 euthanasia, malignant lymphoma was observed in 3 LD females and 1 HD female. Malignancy was observed in multiple tissues in 3 of the animals, but in spleen only in one of the LD animals. The sponsor states that a higher than normal rate of malignant lymphoma with aging is seen in this transgenic strain, with greater frequency in females. They contend that with the age of the F1 generation at PND 357 these findings are likely a background, age-related change, unrelated to inebilizumab. (The sponsor provided references from published literature but no relevant historical data to support this claim.)

Text Table 21
Incidence of Selected Histopathologic Findings, PND 50 Necropsy (Subgroup 2A)

	Males			Females		
Dosage (mg/kg/dose):	**0**	**3**	**30**	**0**	**3**	**30**
Spleen [a]	**10**	**10**	**10**	**10**	**10**	**10**
White pulp: reduced size/cellularity	1	10	10	0	10	10
Minimal	0	0	0	-	1	0
Mild	0	0	0	-	0	1
Moderate	1	6	4	-	6	5
Marked	0	4	6	-	3	4
Lymph node, axillary [a]	**9**	**9**	**10**	**10**	**10**	**9**
Follicles: reduced number/cellularity	3	9	10	3	10	9
Mild	1	0	0	0	0	0
Moderate	2	0	0	2	0	0
Marked	0	0	0	0	0	0
Severe	0	9	10	1	10	9
Lymph node, mandibular [a]	**10**	**9**	**9**	**10**	**9**	**10**
Follicles: reduced number/cellularity	2	9	9	0	9	10
Mild	2	0	0	-	0	0
Marked	0	1	0	-	0	0
Severe	0	8	9	-	9	10
Lymph node, mesenteric [a]	**10**	**10**	**10**	**10**	**10**	**10**
Follicles: reduced number/cellularity	2	10	10	1	10	10
Mild	0	0	0	1	0	0
Moderate	2	0	0	0	1	0
Marked	0	2	0	0	2	3
Severe	0	8	10	0	7	7

[a] Number of tissues examined from each dose group.

F1 Toxicokinetics

Test article levels in F1 pup serum on PND21; TK parameters were not calculated.

Text Table 25
F_1 Pup Serum Concentrations

Dosage Level (mg/kg/dose)	Gender	Number of Animals Represented	Mean MEDI-551 Concentration (µg/mL)
0	Male	12	<0.02
	Female	11	<0.02
3	Male	12	30.42
	Female	12	33.33
30	Male	11[a]	413.87
	Female	12	390.81

[a] = The group mean summary statistics exclude 1 animal (No. 4334-03) whose sample generated no reportable TK result.

Formulation analysis:

Samples of the dosing formulations were collected according to the schedule below.

Text Table 2
Dose Formulation Sample Collection Schedule

Date	Concentration	Stability
22 Apr 2016	All groups	Group 2
03 Jun 2016	All groups	N/A
22 Jul 2016	All groups	N/A
09 Sep 2016	All groups	N/A
10 Jan 2017	Groups 2 and 3	N/A

N/A = not applicable.

All dosing formulation samples were within pre-established acceptance criteria for concentration.

11 Integrated Summary and Safety Evaluation

Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1 kappa (IgG1κ) monoclonal antibody (mAb), developed for treatment of NMOSD. The product is designed to bind the B cell-specific surface antigen CD19 in humans with high affinity and specificity. CD-19 is reported to be expressed on a spectrum of B lymphocytes through development from pro-B cell to plasmablasts as well as some plasma cells.

Pharmacology

A series of pharmacology studies was conducted confirming that inebilizumab binds with high affinity and specificity to human CD19 and not to CD19 in rodents or available nonrodent species. Therefore, the nonclinical program was conducted using a mouse model that expressed human CD19 (huCD19Tg mouse). Studies conducted to characterize this mouse model were submitted to IND (b) (4), and agreement was reached that this model is the most relevant for testing of inebilizumab.

In vitro and in vivo studies were conducted to assess the magnitude, selectivity, duration, and mechanism of inebilizumab-induced B cell depletion. These studies demonstrated that the B-cell depletion is dose-related in magnitude and duration. Immunophenotyping of peripheral blood and bone marrow indicated that the depletion is limited to B lymphocytes and other immune cell populations are not significantly affected. Studies conducted to investigate the mechanism of action of inebilizumab demonstrated that the B-cell depletion occurs via ADCC through binding to Fcγ receptor IIIA.

Toxicology

General toxicology studies were conducted in huCD19Tg mouse with durations of 1, 3, and 6 months in which inebilizumab was administered weekly by IV injection at doses up to 30 mg/kg. (A second 3-month study was conducted using SC administration.) In general, all toxicities observed were considered to be results of the known pharmacological activity of the drug. The B cell depletion was dose-related in magnitude and duration. Near total B-cell depletion was observed in peripheral blood at the higher doses with no significant effect on other immune cell populations.

The studies showed a slightly greater effect (magnitude and duration) in males relative to females. Slightly greater exposure and longer $t_{1/2}$ was observed in males relative to females. Full recovery in the 3-month IV study required 28 and 36 weeks for HD females and males, respectively.

Microscopic findings of reduced cellularity of B-cell regions of the splenic white pulp and reduced B-cell follicles in lymph nodes were consistently observed in all studies and were expected results of the pharmacological activity of inebilizumab. In the 3-month and 6-month studies where sufficient recovery period were used, full resolution of the microscopic findings was observed.

In the longer duration studies (3 and 6 months) a dose-related increase in skin ulceration was observed and was the reason for multiple early deaths. This finding was considered related to the immunosuppression resulting from the B-cell depletion induced by inebilizumab. Skin lesions were not observed at the end of the recovery periods.

In the SC/IV 3-month study, bronchio-alveolar adenomas were observed in 50% (7 of 14) HDIV males during the recovery period. However, the finding was not observed in the 6-month study at the same doses.

Reproductive toxicology

Two reproductive toxicology studies were conducted in the huCD19Tg mouse model: combined male and female fertility and embryofetal development study and a pre-and postnatal development study.

In the fertility and embryofetal study, male and female huCD19 Tg mice received weekly IV injections of inebilizumab at dose levels of 0, 3, or 30 mg/kg beginning 28 days prior to mating for males and 15 days prior to mating for females. The dosing in females was continued until day 15 of gestation.

Near total deletion of B cells in peripheral blood was observed in dams at the time of Cesarean section and in adult males at euthanasia. B cells positive for huCD19 were undetectable in fetal blood from both dose groups accompanied by detectable levels of inebilizumab. At the LD, mean fetal inebilizumab level was slightly higher than mean maternal level (12.0 µg/mL and 10.5 µg/mL, respectively). At the HD, the mean fetal inebilizumab level lower than the mean maternal level (60.9 µg/mL and 196 µg/mL, respectively.)

Evaluation of fertility parameters showed a dose-related decrease in fertility index affecting both the LD and HD groups. Of the 25 pairs of mice in cohabitation for each group, 100% mated successfully. However, of these pairs, the percent pregnant was 96.0, 76.0, and 64% for control, LD, and HD groups, respectively. No other effects on cesarean parameters were observed.

In a pre-and postnatal development study, huCD19Tg mice received IV doses of inebilizumab every 3 days throughout gestation (beginning on GD6) and continuing through lactation. No adverse effects on fetal development were observed. Unscheduled death of dams was observed, but the incidence was similar among groups including the control group. No inebilizumab-related adverse effects were observed in the dams throughout the study. The only effect related to the test article was depletion of B lymphocytes in peripheral blood, which is an expected finding. No effects related to the test article were observed on gestational length or the parturition process.

In the F1 pups, the incidence of postnatal death was similar among groups. No other test article-related effects were observed in postnatal body weight change, physical development, or sexual maturation.

In neurobehavioral evaluations, increased peak response in auditory startle was observed in male HD pups, suggesting an adverse effect on sensory integration in this group. The effect was not observed in female pups. No adverse effects on motor behavior or learning and memory were observed.

However, the neurobehavioral testing in this study is not considered adequate because an insufficient number of animals was tested. In addition to the inadequate number of animals, the maze test used for learning and memory was not conducted appropriately (testing in the Biel maze used only the A path and not the typical A and B paths) and is also, for that reason, not acceptable.

As justification for the reduced number of F1 pups used in neurobehavioral testing, the sponsor states that the CD19 Tg strain of mice "have low pregnancy rates, reduced fecundity, and small litter sizes." Additionally, only the pups in a litter that have the specific genotype can be used. (The sponsor did not offer any explanation for why the single path method was selected for the Biel maze testing.)

Due to the inadequacy of design, the neurobehavioral testing is not considered adequate, and clear conclusions regarding the potential for adverse effect of inebilizumab cannot be drawn from the data. However, in spite of the reduced number of pups evaluated, repeat of the study is not recommended due to the difficulty in obtaining required numbers of offspring with the appropriate genotype.

After weaning, F1 pups showed severely reduced levels of B lymphocytes (tested on PND50; reductions of 97 and 100% for LD and HD pups, respectively). No other immune cell populations were affected. By the end of the study, B-cell levels in F1 pups in the LD and HD groups had achieved levels similar to control. However, when a function immunotoxicity test (TDAR) was conducted beginning on PND 357, pups from both the LD and HD groups showed significant impairment in IgM and IgG response to immunization. These data indicate that, although B cells had achieved normal levels, the function was impaired.

When F1 pups were mated, no effect related to inebilizumab was observed in mating behavior or mating parameters. Litter parameters showed a slightly higher rate of early resorptions and total resorptions, as well as a higher rate of post-implantation loss in the HD group. No malformations were observed in F2 offspring.

Recommendation:

The nonclinical data are adequate for approval of inebilizumab for the intended indication.

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/

BARBARA J WILCOX
04/28/2020 01:29:36 PM

LOIS M FREED
04/28/2020 02:51:15 PM