CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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:	761044
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Applicant's letter date:	SDN 1: 11/25/2015
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Product:	Stelara® (Ustekinumab)
Indication:	Treatment of adult patients with moderately to severely active Crohn's Disease
Applicant:	Janssen Biotech, Inc.
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Jackye Peretz, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Lawrence Allan

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Janssen Biotech Inc. seeks approval of Stelara® (ustekinumab) for the treatment of adult patients with moderately to severely active Crohn's Disease. Stelara® BLA was submitted under the 505(b)(1) pathway. Stelara® was approved for the treatment of adults with moderate to severe plague psoriasis and/or active psoriatic arthritis (PsA) in the United States under BLA 125261 on September 25, 2009.

1.2 Brief Discussion of Nonclinical Findings

The Applicant did not conduct any new nonclinical studies to support the current biologics licensing application. The Applicant is cross-referencing all nonclinical information previously submitted under BLA 125261 that is supportive of the proposed indication and new intravenous formulation of Stelara®. These studies were previously reviewed for BLA 125261 dated November 28, 2008 (J. Yao, Ph.D.; Dermatology and Dental Products).

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, no approvability issues are identified for this BLA.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Applicant's Proposed Version:

8.1 Pregnancy

Risk Summary

(b) (4)

Animal Data
Ustekinumab was tested in two embryo-fetal development toxicity studies (b) (4) in (b) (4) (b) (4) cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses (b) (4) from pregnant monkeys that were administered ustekinumab (b) (4) during the period of organogenesis (b) (4) Serum concentrations of ustekinumab in pregnant monkeys were > 100 times the serum concentration in patients treated with 90 mg of ustekinumab weekly for 4 weeks.

Evaluation:
1. The Applicant has removed the paragraph below with no justification provided. The animal data should stay in this section.

"In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly (b) (4) from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab related effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age."

(b) (4)

3. The remaining labeling is acceptable.

Recommended Version:

8.1 Pregnancy

Risk Summary
(b) (4)

Animal Data
Ustekinumab was tested in two embryo-fetal development toxicity studies (b) (4) in (b) (4) (b) (4) cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses (b) (4)

(b) (4) old from pregnant monkeys that were administered ustekinumab (b) (4) during the period of organogenesis (b) (4) Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated with (b) (4) 90 mg subcutaneous dose of ustekinumab weekly for 4 weeks.

In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly greater than 100 times the human subcutaneous exposure from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab related effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.

Applicant's Proposed Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of STELARA®. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration (twice weekly) (b) (4) at doses up to 50 mg/kg, prior to and during early pregnancy.

Evaluation:

1. The Applicant has stated that the addition of the phrase (b) (4) to the sentence regarding the fertility study in mice pertains to (b) (4) (b) (4) in error. The Applicant proposes to revise the statement to reflect the currently approved label text as shown below and will provide this revision to the proposed label update after receipt of the Agency's draft labeling (Non-clinical/Response to Information Request; 5/23/2016).

"No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration (twice weekly) (b) (4) (b) (4) at doses up to 50 mg/kg (b) (4) prior to and during early pregnancy."

2. The remaining labeling is acceptable.

Recommended Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of STELARA®. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration (twice weekly) (b) (4) (b) (4) at doses up to 50 mg/kg (b) (4) prior to and during early pregnancy.

Applicant's Version:

13.2 Animal Toxicology and/or Pharmacology

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection.

Evaluation: This section of the labeling is acceptable.

2 Drug Information

2.1 Drug

CAS Registry Number: 815610-63-0

Generic Name: ustekinumab

Code Name: CNT-1275, 12B75

CAS Index Name: Immunoglobulin G1, anti- (human interleukin 12 p40 subunit) (human monoclonal CNTO 1275 γ1-chain), disulfide with human monoclonal CNTO 1275 κ-chain, dimer.

Molecular Formula/Molecular Weight: 1326 Amino acids/ 148 to 149 kD

Structure or Biochemical Description:
The amino acid sequence of CNTO 1275 deduced from the DNA sequence for the molecule is shown below for the heavy and light chains, respectively.

Heavy Chain Amino Acid Sequence

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                                        CDR-H1
EVQLVQSGAE  VKKPGESLKI  SCKGSGYSFT  TYWLGWVRQM  PGKGLDWIGI  50
      CDR-H2
MSPVDSDIRY  SPSFQGQVTM  SVDKSITTAY  LQWNSLKASD  TAMYYCARRR  100
 CDR-H3
PGQGYFDFWG  QGTLVTVSSS  STKGPSVFPL  APSSKSTSGG  TAALGCLVKD  150
YFPEPVTVSW  NSGALTSGVH  TFPAVLQSSG  LYSLSSVVTV  PSSSLGTQTY  200
ICNVNHKPSN  TKVDKRVEPK  SCDKTHTCPP  CPAPELLGGP  SVFLFPPKPK  250
DTLMISRTPE  VTCVVVDVSH  EDPEVKFNWY  VDGVEVHNAK  TKPREEQYNS  300
TYRVVSVLTV  LHQDWLNGKE  YKCKVSNKAL  PAPIEKTISK  AKGQPREPQV  350
YTLPPSRDEL  TKNQVSLTCL  VKGFYPSDIA  VEWESNGQPE  NNYKTTPPVL  400
DSDGSFFLYS  KLTVDKSRWQ  QGNVFSCSVM  HEALHNHYTQ  KSLSLSPGK   449
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Light Chain Amino Acid Sequence

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                                  CDR-L1
DIQMTQSPSS  LSASVGDRVT  ITCRASQGIS  SWLAWYQQKP  EKAPKSLIYA  50
 CDR-L2                                    CDR-L3
ASSLQSGVPS  RFSGSGSGTD  FTLTISSLQP  EDFATYYCQQ  YNIYPYTFGQ  100
GTKLEIKRTV  AAPSVFIFPP  SDEQLKSGTA  SVVCLLNNFY  PREAKVQWKV  150
DNALQSGNSQ  ESVTEQDSKD  STYSLSSTLT  LSKADYEKHK  VYACEVTHQG  200
LSSPVTKSFN  RGEC                                          214
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Pharmacologic Class: Interleukin receptor inhibitor, monoclonal antibody

2.2 Relevant INDs, NDAs, BLAs and DMFs

BLA 125261 (Stelara®; DDDP; psoriasis)

2.3 Drug Formulation

The CNTO 1275 final vialed product (FVP) is supplied as a sterile solution in a single [redacted] Type I glass vial closed with a [redacted] stopper and a [redacted] 13 mm aluminum seal and plastic light green flip-off button. CNTO 1275 FVP is manufactured in two doses, a 45 mg vial (0.5 mL) and a 90 mg vial (1.0 mL). The quantitative compositions of all components in CNTO 1275 FVP, expressed as mg per dose, are shown in Table 1 (from page 1 of "Description and Composition of the Drug Product-FVP"; BLA 125261).

Table 1: Composition of CNTO 1275 90 mg and 45 mg FVP.

Component	90 mg Dose Amount Per Dose (mg)	45 mg Dose Amount Per Dose (mg)	Concentration
CNTO 1275	90	45	[redacted]
Sucrose	76	38	
L-histidine	1.0	0.5	
Polysorbate 80	0.04	0.02	
[redacted]			

[redacted]

The CNTO 1275 drug product (DP) is supplied as a sterile solution in a single-use, pre-filled syringe (PFS). The PFS is composed of a [redacted] Sterile, Clean, [redacted] 1 mL long syringe with a fixed, 27 guage half-inch stainless steel needle, stoppered with a [redacted] gray plunger stopper. The needle is covered with [redacted] (dry natural rubber) [redacted] CNTO 1275 PFS is manufactured in two dosages, a 45 mg/syringe (0.5 mL) and a 90 mg/syringe (1.0 mL). CNTO 1275 PFS with 45 mg (0.5 mL) or 90 mg (1.0 mL) doses will be assembled into an [redacted] for subcutaneous administration by a health care professional or a patient. The quantitative composition of CNTO 1275 PFS, expressed as mg per dose, is shown in Table 2 (from page 1 of "Description and Composition of Drug Product- PFS"; BLA 125261).

Table 2: Composition of CNTO 1275 90 mg and 45 mg PFS.

Component	90 mg Dose Amount Per Dose (mg)	45 mg Dose Amount Per Dose (mg)	Concentration
CNTO 1275	90	45	(b) (4)
Sucrose	76	38	
L-histidine[a]	1.0	0.5	
Polysorbate 80	0.04	0.02	
(b) (4)			
(b) (4)			

The ustekinumab final vialed product for intravenous administration [FVP (IV)] is supplied as a single-use, sterile solution designed to deliver 130 mg of ustekinumab in a 30 mL, Type-1 glass vial. The vials are stoppered with 20-mm (b) (4) coated (b) (4) (b) (4) stoppers and sealed with 20-mm aluminum flip-off seals. The vials are filled at a target volume of (b) (4) mL per vial to deliver no less than 26.0 mL, the nominal deliverable volume, for a 130 mg dose. The composition of the drug product is shown in Table 3 (from page 1 of "Description and Composition of the Drug Product-FVP (IV)"; BLA 761044).

Table 3: Composition of Ustekinumab FVP (IV).

Component	Grade	Function	Mg/Vial	Concentration (mg/mL)
ustekinumab	NA	Active	(b) (4)	(b) (4)
L-Histidine	USP/Ph. Eur/JP	(b) (4)		
L-Histidine Hydrochloride Monohydrate	Ph. Eur./JP			
Sucrose	NF/Ph. Eur./JP			
Polysorbate 80	NF/Ph. Eur./JP			
L-Methionine	USP/Ph. Eur./JP			
EDTA disodium salt dihydrate[b]	USP/Ph. Eur./JP			
(b) (4)				
(b) (4)				

2.4 Comments on Novel Excipients

The excipients used in the ustekinumab FVP (IV) drug product are listed in Table 4 below (from page 1 of "Control of Excipient/Compendial/Specifications"; BLA 761044). There are no novel excipients in the proposed drug product.

Table 4: Excipients used in the ustekinumab FVP (IV) drug product.

Material	Specification
L-Histidine	USP/Ph. Eur./JP
L-Histidine hydrochloride monohydrate	Ph. Eur./JP
Sucrose	NF/Ph. Eur./JP
Polysorbate 80	NF/Ph. Eur./JP
L-Methionine	USP/Ph. Eur./JP
EDTA disodium salt dihydrate[a]	USP/Ph. Eur./JP
[redacted] (b) (4)	

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern. There were no changes in the FVP(IV) drug product specifications from the previously approved product under BLA 125261. All analyses for the intended batches of the commercial drug product for the single IV induction dosing for Crohn's Disease were within the acceptance criteria or below the specified acceptance limit. Therefore, they are acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

This 505(b)(1) Biologics License Application proposes the use of Stelara® in adults for the treatment of moderately to severely active Crohn's Disease who have 1) failed or were intolerant to immunomodulators or corticosteroids but never failed [redacted] (b) (4) or 2) failed or were intolerant to [redacted] (b) (4) The recommended adult dosage for the Crohn's Disease indication is a single intravenous (IV) infusion induction dose using weight based tiers (approximately 6 mg/kg), followed by maintenance subcutaneous (SC) dosing of 90 mg administered eight weeks after the initial IV dose, then every eight [redacted] (b) (4) weeks thereafter.

2.7 Regulatory Background

None

3 Studies Submitted

The Applicant did not submit any new nonclinical studies to support this biologics licensing application and is cross-referencing all nonclinical information previously submitted under BLA 125261 that is supportive of the proposed indication and new

intravenous formulation. These studies have been reviewed by J. Yao, Ph.D., dated 7/28/2008 (Dermatology and Dental Products; moderate to severe plaque psoriasis).

3.1 Studies Reviewed

None

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

BLA 125261; Jiaqin Yao, Ph.D.; 7/28/2008; Dermatology and Dental Products; moderate to severe plaque psoriasis

4 Pharmacology

No new studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

No new studies were submitted.

6 General Toxicology

No new studies were submitted.

7 Genetic Toxicology

No new studies were submitted.

8 Carcinogenicity

No new studies were submitted.

9 Reproductive and Developmental Toxicology

No new studies were submitted.

10 Special Toxicology Studies

No new studies were submitted.

11 Integrated Summary and Safety Evaluation

Janssen Biotech Inc. seeks to market Stelara®, an interleukin receptor inhibitor, monoclonal antibody, for the treatment of adult patients with moderately to severely (b) (4) Stelara® is approved for the treatment of adults with moderate to severe plaque psoriasis and/or active psoriatic arthritis (PsA) in the United States under BLA 125261 (Janssen Biotech, Inc.). The Applicant's proposed drug product differs from the approved product with respect to the indication and the new 130 mg/26 mL intravenous formulation.

The Applicant did not submit any new nonclinical studies to support the biologics licensing application and is cross-referencing all nonclinical information previously submitted and reviewed under BLA 125261. A summary of the nonclinical studies is provided below from the BLA 125261 Pharmacology review, with additional information included for the proposed indication as appropriate (J.Yao; BLA 125261; Pharmacology Review; 7/28/2008; Dermatology and Dental Products; moderate to severe plaque psoriasis).

IL-12 and IL-23 cytokines are comprised of a shared p40 subunit and a subunit unique to each cytokine, p36 for IL-12 and p19 for IL-23. Inappropriate, increased expression of IL-12 and IL-23 might be linked to immune-mediated diseases including Crohn's Disease (CD), making the cytokines as targets for immunotherapy for CD. Ustekinumab is a fully humanized lgG1 kappa monoclonal antibody against the p40 subunit of IL-12 and IL-23. Ustekinumab binds to the shared p40 protein subunit and inhibits IL-12 and IL-23 bioactivity by preventing their interaction with their IL-12Rβ1 receptor protein expressed on the surface of immune cells. Through this mechanism of action, ustekinumab neutralizes IL-12 and IL-23-mediated cellular responses. Ustekinumab was shown to have comparable binding and neutralization activity against human and cynomolgus monkey IL-12 and IL-23. Pharmacodynamic activity studies indicated that cynomolgus monkey was the pharmacologically relevant toxicology species for ustekinumab. In addition, data supported that mice were relevant toxicology species for an analogous antibody against mouse IL-12/IL-23p40, CNTO 3913.

Pharmacokinetic/toxicokinetic studies with ustekinumab (CNTO 1275) have been conducted in monkeys following single and multiple intravenous or subcutaneous injections at doses ranging from 1.0 to 50 mg/kg. The highest dose in monkeys in toxicity studies with CNTO 1275 is 7.7 times (based on mg/kg) the recommended IV induction clinical dose in Crohn's disease patients (approximately 6 mg/kg based on administration of a 390 mg dose to a 60 kg Crohn's patient). Toxicokinetic evaluations confirmed high CNTO 1275 exposure of monkeys in the toxicity studies.

Following single and multiple IV infusions, the mean T_{max} occurred 2 hours after injection. C_{max} concentration increased following repeated weekly dosing, indicating CNTO 1275 accumulation\ in the serum.

Following single and multiple SC administrations, the mean T_{max} ranged from 2 to 7 days. Mean C_{max} and AUC values increased in an approximately dose-proportional manner. The mean half-life ($t_{1/2}$) values ranged from 2-3 weeks following multiple subcutaneous injections of CNTO 1275 in monkeys.

Following repeated weekly IV infusions over four weeks, C_{max} supra-proportionally increased, with CNTO 1275 accumulating 2-fold in the serum over four weeks of dosing. The mean C_{max} following a 50 mg/kg weekly IV dosing in monkeys (4031 µg/mL) was over 32-fold higher than the mean C_{max} following the single IV induction infusion at Week 0 (125.2 µg/mL), and 630-fold higher than the mean C_{max} at the end of induction (Week 8), in subjects with Crohn's Disease.

Following repeated, twice-weekly SC dosing, CNTO 1275 showed 5 to 10-fold accumulation of drug and steady state was achieved in about 13 weeks. The mean steady-state C_{max} value following a 45 mg/kg twice-weekly SC dose in monkeys (2347 µg/mL) was over 1000-fold and 2680-fold higher than the median, steady-state serum ustekinumab concentrations over time following maintenance treatment with q8w 90 mg SC dosing (2.24 µg/mL) or q12w 90 mg SC dosing (0.76 µg/mL), respectively, in subjects with Crohn's Disease.

Because of the long half-lives, different treatment regimens, accumulation, and/or possibly not-enough time-points to measure the serum CNTO 1275 concentrations in monkeys and patients, the comparison between monkeys and patients on systemic exposure levels may not be accurate. However, the serum concentrations attained were well in excess of those required for complete inhibition of IL-12/IL-23 activity based on in vitro activity evaluations and reported serum concentrations of IL-12/IL-23p40 in monkeys and humans.

Anti-CNTO 1275 antibody development was examined in single and repeat dose SC studies in cynomolgus monkeys, but was not evaluated in the IV studies due to the high serum concentration of CNTO 1275. Anti-CNTO 1275 antibodies were detected in single dose studies but not in multiple dose studies, which may have been due to the substantial presence of circulating CNTO 1275 during the observation period or possible immune tolerance induction. However, in the embryo-fetal development and pre- and postnatal development toxicity study, low levels of antibody against CNTO 1275 were detected in 3 out of 20 control (PBS-treated) monkeys and CNTO 1275 was detected in the pretreatment serum samples of 2 out of 20 animals in the 22.5 mg/kg group and 1 out of 20 animals in the 45 mg/kg group.

CNTO 1275 has been tested in cynomolgus monkeys at doses up to 45 mg/kg by intravenous administration weekly for up to 1 month or by subcutaneous administration twice weekly for up to 6 months (26 weeks). Safety pharmacology endpoints were incorporated into the design of toxicology studies. Potential effects on the cardiovascular/respiratory system were evaluated following single and repeated dosing with CNTO 1275 by performing electrocardiograms (ECGs), blood pressure, heart rate, and respiratory rate measurements. Potential effects on the central nervous system were evaluated by daily clinical observations and by measurement of rectal body temperature. There were no treatment-related effects on these safety pharmacology parameters. No adverse findings were noted in ECG recordings in 6-month old juvenile monkeys whose respective dams had been exposed to CNTO 1275 during organogenesis resulting in high levels of exposure to CNTO 1275 throughout the 6 month postnatal observation period. No abnormal macroscopic/microscopic cardiac findings were noted in general or developmental toxicity studies.

In the repeated IV injection study, cynomolgus monkeys were treated with doses of 9 or 45 mg/kg CNTO 1275 once weekly for four weeks. The animals were euthanized on Day 29 (n=3/sex/group) or Day 59/60 (n=2/sex/group). There were no treatment related effects on mortality, clinical signs, body weight, food consumption, body temperature, indirect blood pressure, electrocardiograms, physical and ophthalmic evaluations, coagulation, serum chemistry, organ weight, and macroscopic or histopathologic evaluations.

In the repeated SC injection study, cynomolgus monkeys were treated with doses of 22.5 or 45 mg/kg CNTO 1275 twice weekly for 26 weeks. There were no treatment related effects on survival, clinical signs, body weight, food consumption, blood pressure, physical, ophthalmic, and electrocardiographic examinations, clinical pathology, macroscopic observations, organ weights, and. histopathological examinations. There were no treatment-related differences in histomorphology or CD3 and CD20 immunohistostaining of the lymphoid organs, and no treatment-related effects on functional immune responses measured by KLH analysis and circulating lymphocyte subpopulation. No delayed signs of toxicity were observed in the 12-week recovery groups monkeys. However, one out of 10 monkeys administered 45 mg/kg CNTO 1275 for 26 weeks exhibited signs of bacterial enteritis.

No genetic toxicology studies have been conducted with CNTO 1275.

Nonclinical carcinogenicity studies have not been conducted with CNTO 1275. No tumors or histopathological evidence of pre-neoplastic changes were observed in organs or tissues examined following subcutaneous administration of CNTO 1275 to monkeys at doses up to 45 mg/kg twice weekly for six months followed by a 3-month recovery period. However, CNTO 1275 is a selective immunosuppressant and the risk of malignancy in patients is a safety concern for immunosuppressive drugs. Immunosuppressive agents have the potential to increase the risk of malignancy. Literature data showed that administration of murine IL-12 exerted an anti-tumor effect in mice that contained transplanted tumors. Literature data furthermore demonstrated that host defense to neoplasia decreased in IL-12/IL-23p40 knockout mice or in mice treated with anti-IL-12/IL-23p40 antibody. Therefore, long-term administration of CNTO 1275 may have the potential to increase the risk of malignancy in patients. At this time, it appears that another 2-year carcinogenicity study with IL-12/IL-23p40-depleted mice will not be very informative. Adequate labeling on animal data from literature and post-marketing patient monitoring of malignancy may be sufficient at this time.

A male fertility study, two embryo-fetal development toxicity studies, and an embryo-fetal development and pre- and post-natal development toxicity study have been conducted in cynomolgus monkeys at doses up to 45 mg/kg CNTO 1275 via SC or 50 mg/kg CNTO 1275 via IV administration. A female fertility study was conducted in mice using an analogous IL-12/IL-23p40 antibody. In the male fertility study, three groups of only six male monkeys (should have included at least 12 male monkeys per group) were administered subcutaneous doses of 0, 22.5, and 45 mg/kg CNTO 1275 twice

weekly prior to mating and during the mating period for 13 weeks, followed by a 13-week treatment-free period. No mortality or CNTO 1275-related effects on clinical observations, body weight, or food consumption were observed. There were no treatment related effects on semen color or volume, sperm counts, viability, activity, or morphology, mating behavior based on evaluations of time elapsed until mounting, number of mountings, mounting positions, or ejaculation, and serum inhibin B or testosterone levels. Fertility and pregnancy outcomes were not evaluated in mated females. Toxicokinetic analyses confirmed that the expected high levels of systemic CNTO 1275 exposure were attained.

In the female fertility study in mice using an analogous IL-12/IL-23p40 antibody (CNTO 3913), SC administration of CNTO 3913 at doses up to 50 mg/kg, twice weekly, beginning 15 days before cohabitation (maximum 21 days) and continuing through gestational day (GD) 7, did not cause any treatment-related effects on mortality, clinical signs, body weight, estrous cycling, and necropsy in female mice. There were no treatment related effects on mating parameters (numbers of days in cohabitation, fertility index, mice that mated, and mice with confirmed mating dates during the first or second week of cohabitation), corpora lutea, implantations, viable and nonviable embryos, and percent nonviable embryos per litter. TK analyses confirmed exposure of mice to CNTO 3913 and showed dose proportional increases in exposure and AUC (0-3d) and accumulation of CNTO 3913 following repeated twice weekly subcutaneous dosing.

In the IV administered, embryo-fetal development toxicity study, three groups of 12 pregnant cynomolgus monkeys were administered IV doses of 0, 10, or 50 mg/kg CNTO 1275, once weekly, during the organogenesis period from GD20 to GD50, to evaluate potential adverse effects on the development of the conceptus. No maternal deaths occurred. The frequencies of abortion/embryonic death in the control, 10, and 50 mg/kg groups were similar across treatment groups. No treatment-related abnormalities were noted in clinical signs, body weight, food consumption or immunological examinations. No fetal deaths occurred and no treatment related effects on fetal weight, placental weight, external measurements, organ weight, immunological examinations, immunohistochemistry examinations, external fetal appearance, or placental, visceral and skeletal findings were observed at cesarean sectioning between GD100 and GD102.

The analyses of maternal CNTO 1275 serum concentrations indicated that CNTO 1275 accumulated in the serum over the 5-week dosing period for both the 10 and 50 mg/kg treatment groups. The maternal C_{max} serum concentrations of CNTO 1275 during the study were 599 ± 152 µg/mL and 3279 ± 590 µg/mL for the 10 and 50 mg/kg treatment groups, respectively. These values were observed just after the fifth (last) dose administration. The mean CNTO 1275 serum concentrations for the fetal samples collected at cesarean section on Day 100 of gestation were 9.33 ± 4.77 µg/mL and 21.27 ± 11.83 µg/mL for the 10 and 50 mg/kg treatment groups, respectively. These results indicate that the fetuses were exposed to CNTO 1275 during the period of organogenesis (Days 20 to 50 of gestation) and continued to be exposed to CNTO 1275 until the end of study (Day 100 of gestation). No antibodies to CNTO 1275 were detected in the sera during the study.

In the SC administered, embryo-fetal development and pre- and post-natal development toxicity study, three groups of 20 pregnant cynomolgus monkeys were administered subcutaneous doses of 0, 22.5, or 45 mg/kg CNTO 1275 twice weekly from GD20 to GD33 after delivery, to evaluate potential adverse effects of CNTO 1275 on the pregnant/lactating female and on development of the conceptus. No dam died during this study and no CNTO 1275-related abnormalities were observed in dams in clinical signs, body weight, food consumption, hematology, or serum biochemistry. Fetal losses occurred in six control animals (GDs 27, 54, 123, 155, 157, and 172), in six 22.5 mg/kg treated animals (GDs 31, 40, 48, 90, 143, and 154), and in five 45 mg/kg-treated animals (GDs 27, 30, 70, 142, and 162). Neonatal deaths occurred in one 22.5 mg/kg-treated animal (Day 6 afterbirth) and in one 45 mg/kg-treated animal (GD 162). The incidence of fetal loss in the treatment groups at the early/middle/late stages of gestation and stillbirth was close to or less than that in the saline control group and within that of historical control values for the test facility, and was therefore considered to be incidental and not related to CNTO 1275 treatment. No CNTO 1275-related abnormalities were observed in the neonates from birth through six months of age in clinical signs, body weight, hematology, or serum biochemistry. Functional development until weaning, as measured by pupil reflex, Preyer reflex, pain response, and grip strength evaluated in F1 animals between Day 30 and Day 40 after birth, was not affected by CNTO 1275 treatment. Functional development after weaning, as measured by electrocardiographic recordings and ophthalmology examinations conducted at five to six months of age in the F1 animals, was not affected by CNTO 1275 treatment. Morphological development in the F1 animals, measured on Days 30, 90, and 180 after birth, showed no CNTO 1275 treatment related changes. Gross and histopathological examinations of F1 animals at six months of age revealed no CNTO 1275 treatment-related changes. Immunological development in the F1 generation, as determined by flow cytometry analysis of peripheral blood lymphocytes (CD3, CD4, CD8, and CD20) on Days 62, 92, and 180 after birth; humoral immune competence by antibody response to KLH and tetanus toxoid; and cellular immune competence by delayed-type hypersensitivity reaction to tetanus toxoid between Day 140 and Day 168 after birth, and immunohistological analysis of lymphoid tissues (spleen, thymus, lymph nodes, and bone marrow) on Day 180 after birth showed no CNTO 1275 treatment-related changes.

Maternal and fetal CNTO 1275 exposure increased with dose from 22.5 to 45 mg/kg following twice-weekly SC administration to the dams from Day 20 of gestation to Day 33 of lactation. C_{max} values in the dams were 1591 and 3048 µg/mL in the 22.5 and 45 mg/kg groups, respectively. Terminal half-life values in the dams and the fetuses were comparable in both dose groups (18 to 19 days). Steady-state conditions were reached in the dams by Day 76 to Day 104 of gestation. CNTO 1275 was present at low concentrations in breast milk on Days 14 and 24 of lactation and concentration increased with dose (1.43 to 1.64 µg/mL and 3.12 to 3.18 µg/mL in the 22.5 and 45 mg/kg groups, respectively). None of the CNTO 1275-treated dams (treated with 22.5 and 45 mg/kg) were detected as positive for antibodies to CNTO 1275. However, the presence of drug in the samples could have interfered with detection of antibodies to CNTO 1275 in some animals.

CNTO 1275 was also tested in one other embryo-fetal development toxicity study in which administration of up to 45 mg/kg in pregnant cynomolgus monkeys subcutaneously on GDs 20, 23, 27, 30, 34, 37, 41, 44, 48, and 51 did not cause any significant adverse developmental effects.

In the local tolerance study, subcutaneous administration of CNTO 1275 in monkeys at a dose of 45 mg/kg twice weekly for three weeks did not cause treatment-related effects on mortality, clinical observations, physical examination findings, hematology, coagulation, or serum chemistry. All treatment groups (vehicle control, negative control, and CNTO 1275) had transient minimal to mild macroscopic signs of local irritation, primarily edema during the dosing period of this study. However, histopathological evaluation of the injection sites revealed no findings in the CNTO 1275 and vehicle control groups.

No unexpected binding of CNTO 1275 to normal human tissues was observed in tissue cross-reactivity studies. IV administration of CNTO 1275 at 45 mg/kg on two occasions did not cause adverse clinical signs, and did not affect or exacerbate asthmatic responses in the monkey asthma model studies.

Based on mechanism of action and roles of IL-12/IL23, immunotoxicity evaluations have been incorporated into general toxicity and developmental toxicity studies. However, CNTO 1275 treatment was not associated with immunotoxicity or immunosuppression in monkeys. CNTO 1275 treatment did not cause toxicologically significant effects on functional immune response to a neoantigen or delayed type hypersensitivity responses, did not deplete or otherwise alter lymphocyte subpopulations, and did not reduce *ex vivo* lymphoproliferative responses to T-cell mitogens. There were no CNTO 1275-related macroscopic observations or adverse effects on organ weights at necropsy, no CNTO 1275-related histopathology findings observed in lymphoid tissues of juvenile, young adult, or adult monkeys, and no altered distribution of T and B lymphocytes in lymphoid tissue.

Overall, there are no nonclinical safety issues for the drug substance (ustekinumab) or drug product, Stelara®. However, the Applicant should be asked to revise the labeling as recommended.

12 Appendix/Attachments

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACKYE R PERETZ
07/19/2016

SUSHANTA K CHAKDER
07/19/2016