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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

Pharmacology/Toxicology Supervisory Memorandum

BLA number: 761032
SDN/date/type of submission: 1 / November 16, 2015/ New BLA
Applicant: Valeant Pharmaceuticals Luxembourg Sarl
Supervisor name: Barbara Hill
Division name: Division of Dermatology and Dental Products
Drug: SILIQ (brodalumab)
Pharmacologic class: Human interleukin 17 receptor A antagonist
Indication: Moderate to severe plaque psoriasis

General comments:

- I concur with the overall assessment and conclusions contained in Dr. Carmen Booker's Pharmacology/Toxicology review for this biologic product.
- I concur that there are no nonclinical approval issues for this biologic product and that this BLA is approvable from a Pharmacology/Toxicology perspective.
- I concur that there are no nonclinical Post-Marketing Requirements recommended for this BLA.
- I concur with the recommended nonclinical labeling changes proposed by Dr. Booker for SILIQ contained in section 1.3.3 of her review which include:
 - Pharmacologic Class designation of "human interleukin 17 receptor A antagonist"
 - The revisions proposed for Sections 8.1, 8.2, 8.3, 12.1, 13.1 and 13.2 of the label

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/s/

BARBARA A HILL
07/13/2016

**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: 761032
Supporting document/s: SDN 1
Applicant's letter date: November 16, 2015
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Product: Brodalumab (140 mg/mL), 1.5 mL pre-filled syringe
Indication: Moderate-to-severe plaque psoriasis
Applicant: Valeant Pharmaceuticals Luxembourg Sarl
Review Division: DDDP
Reviewer: Carmen Booker, PhD
Supervisor/Team Leader: Barbara Hill, PhD
Division Director: Kendall Marcus, MD
Project Manager: Strother Dixon

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

SILIQ (brodalumab) is a monoclonal IgG2 antibody that binds with high affinity to human IL-17 receptor A (IL-17RA). The sponsor is seeking approval of brodalumab for the treatment of moderate-to-severe psoriasis. The proposed dosing regimen is 210 mg subcutaneously at weeks 0, 1, and 2, followed by 210 mg every 2 weeks thereafter. The proposed drug product presentation is a 1.5 mL pre-filled syringe.

Brodalumab is a human monoclonal antibody of the IgG2 subclass. It binds with high affinity to human IL-17RA and blocks the activity of IL-17A, IL-17F, IL-17A/F heterodimer, and IL-25. IL-17RA is found on a variety of cells including fibroblasts, epithelial cells and monocytes. IL-25 is associated with Th2-type inflammatory processes and is produced by epithelial cells, Th2 cells, eosinophils, and basophils. IL-17A, IL-17F and IL-17A/F are produced by Th cells and innate immune cells. These cytokines also induce proinflammatory mediators from epithelial cells and fibroblasts that promote tissue inflammation and destruction as well as the maturation of neutrophils and dendritic cells.

1.2 Brief Discussion of Nonclinical Findings

In cynomolgus monkeys dosed with 0, 10, 25 or 90 mg/kg/dose SC brodalumab weekly for six months, mild skin changes and histopathology (MD and HD), increased neutrophil counts (HD) and decreased albumin/globulin ratios (MD and HD) were observed. These changes were at least partially reversible during the recovery period. The NOAEL for this study was determined to be 90 mg/kg/dose.

Three groups of 16-19 pregnant cynomolgus monkeys were administered weekly SC injections of brodalumab (0, 25, 90 mg/kg) from GD 20 to parturition to evaluate potential adverse effects of brodalumab on the pregnant female and on development of the infant. No dam died during this study, and no brodalumab-related abnormalities were observed in infants. However, maternal brodalumab treatment was associated with neonatal deaths (25, 90 mg/kg) and maternal neglect (90 mg/kg). Under the experimental conditions, a NOAEL for prenatal and postnatal development could not be determined.

1.3 Recommendations

1.3.1 Approvability

BLA 761032 is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the Siliq label text. Recommended

revisions for the nonclinical information contained in Section 8 of the label are made below. Refer to the clinical review for recommended revisions for the clinical information contained in Section 8 of the label. A clean copy of these revised labeling sections is provided in the Appendix as Appendix #2.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

SILIQ™ is a human interleukin-17 Receptor A (IL-17RA) antagonist, indicated for the treatment of adults with moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. (1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no (b) (4) data on SILIQ™ use in pregnant women. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of brodalumab during organogenesis through parturition at doses up to 26 times the maximum recommended human dose (MRHD). (b) (4)

(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk (b) (4) of major birth defects and miscarriage in clinically recognized pregnancies is 2 (b) (4) to 4% and (b) (4) 15 (b) (4) to 20% (b) (4), respectively.

Data

Animal Data

A combined embryofetal development and pre- and post-natal development study was conducted in (b) (4) cynomolgus monkeys, administered brodalumab. (b) (4) No brodalumab-related effects on embryofetal toxicity or malformations, or on morphological, functional or immunological development (b) (4) were observed in infants from pregnant monkeys administered weekly (b) (4) subcutaneous (b) (4) doses of (b) (4) brodalumab up to 26 times the

MHRD from the beginning of organogenesis to parturition (on a mg/kg basis of 90 mg/kg/week) [REDACTED] (b) (4)

8.2 Lactation

Risk Summary

[REDACTED] (b) (4) There are no data on the presence of [REDACTED] (b) (4) brodalumab (b) (4) in human milk, the effects on the breastfed infant, or the effects on milk production.

[REDACTED] (b) (4) Brodalumab was detected in [REDACTED] (b) (4) the milk of lactating cynomolgus monkeys [REDACTED] (b) (4)

[REDACTED] (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SILIQ and any potential adverse effects on the breastfed [REDACTED] (b) (4) infant from SILIQ or from the underlying maternal condition.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brodalumab is a human monoclonal IgG2 antibody that selectively binds [REDACTED] (b) (4) to human IL-17RA and [REDACTED] (b) (4) inhibits its interactions with [REDACTED] (b) (4) cytokines IL-17A, IL-17F, IL17C, IL-17A/F heterodimer and IL-25, [REDACTED] (b) (4)

[REDACTED] (b) (4) IL-17RA is a protein expressed on the cell surface and is a required component of receptor complexes utilized by multiple IL-17 family cytokines. [REDACTED] (b) (4)

(b) (4) - Blocking IL-17RA inhibits IL-17 cytokine-induced responses including the release of proinflammatory cytokines and chemokines (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal (b) (4) studies (b) (4) have not been conducted to evaluate the carcinogenic or mutagenic potential of SILIQ. Published literature is mixed on the potential effects on malignancy risk due to the inhibition of the IL-17RA, the pharmacological action of SILIQ. Some published literature suggests that IL-17A directly promotes cancer cell invasion which suggests a potential beneficial effect of SILIQ. However, other reports indicate IL-17A promotes T-cell mediated tumor rejection which suggests a potential adverse effect by SILIQ. However, inhibition of the IL-17RA with SILIQ has not been studied in these models. Therefore, the relevance of experimental findings in these models for malignancy risk in humans is unknown.

(b) (4)

In cynomolgus monkeys, there were no effects on fertility parameters such as reproductive organs or sperm analysis following subcutaneous administration of brodalumab at dose levels up to 90 mg/kg/week (b) (4) for 6 six months, (26 times the MRHD on a mg/kg basis (b) (4)).

The monkeys were not mated in this study to evaluate effects on fertility.

(b) (4)

Reviewer Note: The Division of Pediatric and Maternal Health (DPMH) suggested the following additions to section 8 of the label:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Human IgG antibodies are known to cross the placenta barrier; therefore, SILIQ may be transmitted from the mother to the developing fetus.

8.2 Lactation

Risk Summary

Due to species specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

Human IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to brodalumab are unknown.

Reviewer conclusion: DDDP Pharm/Tox consulted with Pharm/Tox Associate Directors and recommends that the first sentence in section 8.2 regarding species specific differences not be included. Additionally, DDDP Pharm/Tox believes the other statements added by DPMH are of uncertain value.

2 Drug Information

2.1 Drug

CAS Registry Number: 1174395-19-7

Generic Name: brodalumab

Code Name: AMG 827

Chemical Name: anti IL-17RA monoclonal antibody

Molecular Formula/Molecular Weight: [REDACTED] (b) (4)

Biochemical Description: Brodalumab is an IgG2 human monoclonal antibody consisting of 2 heavy chains and 2 light chains of the kappa subclass. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 292. [REDACTED] (b) (4)

Pharmacologic Class: IL-17 receptor A antagonist, monoclonal antibody

Figure 1. Schematic of Brodalumab Structure



2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 104671

2.3 Drug Formulation

Each sterile prefilled syringe contains 140 mg/mL brodalumab in 30 mM glutamate, 2.4% (w/v) proline, and 0.01% (w/v) polysorbate 20 filled to deliver a volume of 1.5 mL to provide 210 mg of brodalumab.

Table 1. Composition of Brodalumab Drug Product

Component	Grade	Function	Concentration	1.5 mL fill in 2.25 mL syringe
				Quantity
Brodalumab	In house ^a	Active ingredient	140 mg/mL	210 mg
Proline	USP, PhEur, JP	(b) (4)	2.4% w/v	36 mg
Polysorbate 20	NF, PhEur, JPE	(b) (4) ^b	0.01% w/v	0.15 mg
(b) (4) ^b	PhEur, JP		30 mM	6.5 mg
Water for injection	USP, PhEur, JP		qs to target volume	qs to target volume

qs = quantum sufficit

^a Tested to internal specifications as described in 3.2.S.4.1 (Specification).

^b (b) (4) glutamate represents the measured concentration in final drug product as described in 3.2.P.2.1 (Components of the Drug Product [140 mg/mL PFS]).

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

SILIQ is a human IL-17RA antagonist indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. SILIQ is administered as 210 mg by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every two weeks thereafter.

2.7 Regulatory Background

- August 27, 2009 IND submitted
- March 9, 2011 IND Type B Meeting to discuss development plan for psoriasis
- June 15, 2011 IND Type C Meeting to discuss PK/PD modeling analysis
- January 23, 2013 IND Type C Meeting to discuss development plans for two dose presentations
- August 6, 2014 IND Type C Meeting – FDA sent feedback regarding their proposed structure and format of the electronic data package.
- October 27, 2014 IND Type C Meeting to discuss plans to develop two dose presentations
- January 21, 2015 IND Type B Meeting to discuss CMC strategy
- March 25, 2015 IND Type B Meeting to discuss BLA submission
- May 13, 2015 IND Safety Meeting to discuss suicidal ideation observed in clinical studies
- October 21, 2015 pre-BLA Meeting

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology:

AMG 827 Binds to IL-17RA, but not IL-17RB or IL-25. Study Number R20090225. January 7, 2015.

IL-17RA Blockade in a Mouse OVA Asthma Model. Study Number R20090287. January 15, 2014.

IL-25 and IL-17RB Expression in Human Lung Tissue. Study Number R20090288. January 7, 2015.

AMG 827 Inhibits IL-17A-induced Signaling in Rabbit and Human Dermal Fibroblasts. Study Number 110458. May 26, 2009.

Determination of Kinetic Rate and Equilibrium Binding Constants of Human IL-17R fph for AMG 827 via Biacore. Study Number R2006239. September 25, 2014.

Inhibition of ¹²⁵I-Human IL-17 Binding to Human Foreskin Fibroblast Cells by Unlabeled Human IL-17, AMG 827, or Mouse Anti-Human IL-17R-M202 mAb. Study Number R2006240. January 15, 2014.

AMG 827 Cross-reacts with Rabbit IL-17R. Study Number R2006241. February 5, 2010.

AMG827 Binding to Lymphocytes, Monocytes and Neutrophils in Whole Blood. Study Number R2006242. February 3, 2015.

AMG 827 Inhibits the IL-17-Induced Gro α Response in Human Foreskin Fibroblast Bioassays. Study Number R2006244. April 13, 2014.

Assessment of M750 and M751, Rat Anti-Mouse Anti-IL-17RA Antibody Combinations in the IL-17A + TNF α or IL-17F + TNF α Co-stimulation Bioassay. Study Number R2006246. April 13, 2014.

Therapeutic Treatment with Anti-IL17RM750 in the TNFRp55/p75 KO and WT CIA Model. Study Number R2006248. January 7, 2015.

Assessment of Collagen-Induced Arthritis (CIA) in IL-17R KO Mice. Study Number R2006348. December 10, 2014.

Inhibition of ¹²⁵I-Murine IL-17 flag Binding to NIH 3T3 Cells by Unlabeled Murine IL-17 flag and Rat Anti-Murine IL-17R-M750 IgG2b. Study Number R2006447. January 7, 2015.

AMG 827 Inhibits IL-17 Stimulated GRO α Production in Human Lung Fibroblast Cultures. Study Number R20070004. March 19, 2014.

ANG 827 Inhibits IL-17A- and IL-17F-Induced IL-6 Production from Normal Human Dermal Fibroblasts and Normal Cynomolgus Dermal Fibroblasts. Study Number R20070242. January 7, 2015.

Dose Titration of Anti-IL-17R M750 in the DBA/1 WT Model of CIA in a Prophylactic Dosing Regimen Looking at Histopathology, PK Analysis and Serum ELISAs. Study Number R20070264. January 7, 2014.

Cross-Linking AMG 827 Bound to the Surface of Human Fibroblasts Does Not Induce GRO α Secretion. Study Number R2008048. February 29, 2008.

AMG 827 Blockade of IL-25 Induced IL-5 Production in an in vitro Human Peripheral Blood Mononuclear Cell Based Assay. Study Number R20080129. April 25, 2008.

Inhibition of IL-25-induced IL-5 Production from Mouse Splenocytes by Chimeric Anti-Mouse IL-17RA mAb M751. Study Number R20080140. January 7, 2015.

Inhibition of IL-17A- and IL-17F-induced IL-6 production from NIH 3T3 cells by Chimeric Anti-Mouse IL-17RA mAb M751. Study Number R20080147. April 9, 2008.

AMG 827 Inhibits IL-17-induced IL-6 mRNA Production in Normal Human Whole Blood. Study Number R20080191. January 12, 2015.

AMG 827 and 4.224 Inhibit IL-17A, IL-17F, and IL-17A/F-induced GRO α Production from Normal Human Dermal Fibroblasts. Study Number R20090127. October 21, 2014.

AMG 827 Inhibits IL-17C-induced DEFB4 mRNA Expression in Normal Human Epidermal Keratinocytes. Study Number R20120145. January 28, 2015.

Efficacy of IL-17R Blockade in Preventing Psoriasis in FVB K14mIL1F6 Transgenic Mice. Study Number R20090128. July 21, 2011.

AMG 827 Binds to Human IL-17RA but not Human IL-17RC. Study Number R20140114. January 15, 2015.

Secondary Pharmacology:

IL-17RA Deficiency in Mice Prevents Weight Loss Associated with Dextran Sodium Sulfate (DSS)-induced Colitis. Study Number R20090293. September 16, 2014.

Prophylactic Treatment with anti-IL-17RA Antibody, M751, does not Protect Against Colitis in *mdr1a*^{-/-} Mice Infected with *Helicobacter bilis*. Study Number R20090294. October 30, 2014.

Blockade of IL-17RA, IL-17RB, or IL-25, does not Reduce the Severity of Dextran Sodium Sulfate (DSS)-induced Colitis. Study Number R20090295. September 22, 2014.

Prophylactic Inhibition of IL-17RA with M751 does not Attenuate Colitis Induced by the Adoptive Transfer of CD4⁺ CD62L⁺ T Cells into Immunodeficient Mice. Study Number R20090296. September 25, 2014.

Pharmacokinetics:

Method Validation for the Determination of AMG 827 in Cynomolgus Monkey Serum by ELISA. Study Number 108545. December 19, 2007.

Method Validation of the Determination of AMG 827 in Pregnant New Zealand White Rabbit Serum by ELISA. Study Number 111678. April 15, 2009.

Method Validation of an ELISA Assay for the Quantification of AMG 827 in Cynomolgus Monkey Breast Milk. Study Number 113652. June 20, 2011.

Method Validation of an ELISA Assay for the Quantification of AMG 827 in Normal, Infant and Pregnant Cynomolgus Monkey Serum. Study Number 112715. June 20, 2011.

An Electrochemiluminescence Immunoassay for the Detection of Antibodies Against AMG 827 in Pregnant Rabbit Serum using the MSD Imager 6000. Document Number MET-002419. January 27, 2009.

Analytical Method Validation Report for an Electrochemiluminescence Immunoassay for the Detection of Antibodies Against AMG 827 in Pregnant Rabbit Serum using the MSD Sector Imager 6000. Document Number MVR-000343. February 4, 2009.

Analytical Method for an Immunoassay to Detect Antibodies to AMG 827 in Cynomolgus Monkey Serum using the MSD 6000. Document Number MET-001948. September 18, 2009.

Validation of an Immunoassay to Detect Anti-AMG 827 Antibodies in Cynomolgus Monkey Serum on the MSD 6000. Document Number MVR-000157. December 12, 2014.

Analytical Method for a Bioassay for the Detection of Neutralizing Antibodies to AMG 827 in Cynomolgus Monkey Serum. Document Number MET-001938. April 18, 2011.

Validation of a Bioassay for the Detection of Neutralizing Antibodies to AMG 827 in Cynomolgus Monkey Serum. Document Number MVR-000129. March 2, 2007.

A Pharmacokinetic Study with AMG 827 in Male Cynomolgus Monkeys Following Intravenous or Subcutaneous Administration. Study Number 108707. June 14, 2007.

A Pharmacokinetic Study with AMG 827 in Male Cynomolgus Monkeys Following Intravenous or Subcutaneous Administration. Study Number 107054. July 20, 2007.

Repeat Dose Toxicology:

1 Month Subcutaneous and Intravenous Injection Toxicity Study of AMG 827 in Cynomolgus Monkeys with a 13 Week Recovery. Study Number 107059. January 15, 2008.

3 Month Subcutaneous Injection Toxicity Study of AMG 827 in Cynomolgus Monkeys with a 17 Week Treatment-Free Phase. Study Number 107713. September 11, 2008.

6 Month Subcutaneous Injection Toxicity Study of AMG 827 in Cynomolgus Monkeys with a 6-Month Treatment-Free Phase. Study Number 107714. May 28, 2010.

Reproductive and Developmental Toxicology:

Dose Range-Finding Developmental Embryo-Fetal Toxicity and Toxicokinetic Study with AMG 827 via Subcutaneous Injection in Rabbits. Study Number 106489. June 26, 2009.

Maternal, Embryo-Fetal, and Neonatal Toxicity Study of AMG 827 Administered by Subcutaneous Injection to Pregnant Cynomolgus Monkeys with 6-Month Postnatal Evaluation. Study Number 107716. May 23, 2011.

Special Toxicology Studies:

AMG827: Single-Dose Subcutaneous Local Tolerance Test in the Rabbit. Study Number 115263. March 27, 2012.

Cross-Reactivity Study of Biotin-AMG 827 with Normal Human, Cynomolgus Monkey and Rabbit Tissues. Study Number 105786. November 1, 2007.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Brodalumab is a human monoclonal IgG2 antibody expressed in a Chinese hamster ovary cell line. Brodalumab binds to IL-17RA, blocking the activity of multiple IL-17 family cytokines including IL-17A, IL-17A/F, IL-17F, and IL-25. IL-17RA is a transmembrane receptor that is found on many cell types including fibroblasts, epithelial cells and monocytes. Brodalumab does not bind IL-17RB or IL-25 and does not affect IL-25 binding to cell surface expressed IL-17RB. Brodalumab partially inhibits the biologic activity of IL-17C at a high dose.

IL-17A, IL-17F and IL-17A/F are produced by Th17 cells and innate immune cells. These cytokines induce proinflammatory mediators that promote tissue inflammation and have effects on the maturation of neutrophils and dendritic cells. IL-25 is produced by epithelial cells, Th2 cells, eosinophils, and basophils and is usually associated with Th2-type inflammatory diseases like asthma. Increased levels of IL-17 A, IL-17F, IL-17C and Th17 cells have been reported in patients with psoriasis.

Brodalumab does inhibit rabbit IL-17-induced activation of rabbit dermal fibroblasts. However, the potency of brodalumab to block human IL-17-induced activation of human fibroblasts (IC_{50} ; 0.03 $\mu\text{g/mL}$) is 89-fold higher than its ability to block IL-17 activation in the rabbit system (IC_{50} ; 2.67 $\mu\text{g/mL}$). Brodalumab cross-reacts with IL-17R on rabbit monocytes and lymphocytes. Hull-17R fph bound to brodalumab with a k_a of $2.60 \times 10^5 \text{M}^{-1}\text{s}^{-1}$, k_d of $6.22 \times 10^{-5} \text{s}^{-1}$, and K_D of 239 pM. The affinity of the mouse anti-hull-17R M202 mAb and brodalumab for cell surface expressed hull-17R was

approximately 10-fold stronger than that of huIL-17. Brodalumab inhibited IL-6 release from normal human dermal fibroblasts and normal cynomolgus dermal fibroblasts in response to IL-17A or IL-17F stimulation. IC₅₀ values were comparable between human and cynomolgus cells. Brodalumab was shown in normal human epidermal keratinocytes to be an incomplete blocker of IL-17C activity. Brodalumab bound only to murine tail fibroblasts expressing human IL-17RA but did not bind to tail fibroblasts expressing human IL-17RC.

IL-17RA blockade using M750 and M751, two rat anti-mouse IL-17RA neutralizing mAbs, on murine NIH 3T3 fibroblasts was sufficient to prevent IL-17A- and IL-17F-induced IL-6 secretion. Treatment of mice with collagen-induced arthritis with an IL-17R monoclonal antibody was effective at reducing disease progression and severity. Human foreskin fibroblasts stimulated with IL-17A released GRO α , while brodalumab pre-incubation inhibited IL-17A-induced GRO α production. Cross-linking brodalumab prior to stimulation with IL-17A also inhibited GRO α production. Cross-linking brodalumab on the surface of cells in the absence of IL-17A stimulation had no detectable impact on GRO α supernatant concentrations. A chimeric anti-IL-17RA monoclonal antibody inhibited IL-25-induced IL-5 production by mouse splenocytes in a dose dependent manner. At a concentration of 30 μ g/mL, chimeric antimouse IL-17RA mAb M751 fully inhibited IL-17A- and IL-17F-induced IL-6 production from NIH 3T3 cells. IL-6 mRNA production in normal human whole blood was increased 2-6 fold above baseline in the presence of TNF- α and increasing amounts of IL-17. The production of IL-6 mRNA could be suppressed to close to baseline by the addition of increasing amounts of brodalumab.

IL-17R is required for an inflammatory response in the collagen-induced arthritis mouse model. IL-17R KO mice were not as susceptible to clinical, histopathologic, or radiographic evidence of disease compared to the WT control mice. Treatment with anti-mouse IL-17RA significantly reduced airway hyperresponsiveness and multiple parameters of inflammation in a mouse OVA asthma model. Brodalumab inhibited IL-17 induced GRO α production in a dose-dependent manner in human foreskin fibroblast cultures with an IC₅₀ value of 0.004 μ g/mL. Brodalumab inhibited the IL-17-stimulated production of GRO α with an average IC₅₀ of 270 pM. Treatment with an anti-IL17R monoclonal antibody was more effective at reducing skin inflammation in a murine psoriasis model than an anti-IL-17 monoclonal antibody. Both reduced epidermal thickness, parakeratotic scaling, intra-epidermal pustules and epidermal rete ridge formation. Both antibodies reduced expression of many proinflammatory genes.

In an in vitro human peripheral blood mononuclear cell based bioassay, brodalumab was found to inhibit IL-25 induced IL-5 production in a dose dependent manner. The mechanism by which brodalumab inhibits the IL-25 response was found not to involve IL-17A.

4.2 Secondary Pharmacology

IL-17 cytokines have been linked to intestinal inflammation. The sponsor studied C57BL/6 mice deficient for IL-17RA for their susceptibility to the induction of colitis by treatment with dextran sodium sulfate (DSS). Female IL-17RA^{-/-} mice or wild-type C57BL/6 control mice were given 3% DSS in their drinking water for 7 days. IL-17RA^{-/-} mice lost significantly less weight than the wild-type mice. Clinical scores were not different between the two groups of mice. Serum concentrations of G-CSF and IL-13 were reduced in the serum of DSS-treated IL-17RA^{-/-} mice. Ip-10, IL-5, IL-12p70 and IL-17 concentrations were significantly increased in the serum of DSS-treated IL-17RA^{-/-} mice.

In another DSS-induced colitis study, female C57BL/6 mice were given either regular drinking water or 2.5% DSS in their drinking water for 7 days to induce colitis. DSS-treated mice were dosed every other day with anti-IL-17RA antibody, anti-IL-17RB antibody, anti-IL-25 antibody or control IgG1 antibody. Blockade of IL-17RA, IL-17RB, and IL-25 had no impact on clinical scores or colon pathology resulting from DSS-induced colitis.

The sponsor studied mdr1a^{-/-} mice for their susceptibility to *Helicobacter bilis*-induced colitis. Mdr1a^{-/-} mice were gavaged with 1x10⁷ *H. bilis* bacteria twice, one week apart to induce colitis. Mice were then treated with 500 µg of M751 (anti-IL-17RA antibody) or control reagents once weekly. *H. bilis*-infected mdr1a^{-/-} mice treated with M751 had significantly increased clinical scores relative to *H. bilis*-infected mice treated with control IgG1 antibody. Eighty percent of the animals in the M751-treated group either died or were euthanized early due to severe disease. No changes in colon pathology were observed.

An additional study was conducted in immunodeficient mice in which colitis was induced by the adoptive transfer of pathogenic CD4⁺ CD62L⁺ T cells. The mice were then injected intraperitoneally once weekly with nothing, PBS vehicle, 500 µg control IgG1 antibody or 500 µg M751. No significant effects were observed.

4.3 Safety Pharmacology

No independent safety pharmacology studies were conducted. Safety pharmacology endpoints were evaluated in repeat-dose toxicity studies in cynomolgus monkeys.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

A single dose pharmacokinetic study was conducted in cynomolgus monkeys via subcutaneous (SC) or intravenous (IV) dosing at doses of 0.5, 5, and 50 mg/kg brodalumab at a dose volume of 1 mL/kg. Each group consisted of three monkeys.

Dose (mg/kg)		Tmax (hr)	Cmax (ng/mL)	AUClast (hr*ng/mL)	AUCINF (hr*ng/mL)	AUC Extrap (%)	Vz/F (L)	Cl/F (L/hr)	MRT (hr)
0.5	Mean	27	1280	69700	74200	8.74	0.681	0.0222	45
	SD	20	808	43400	41000	7.72	0.522	0.0112	9.5
	CV%	75	63.1	62.3	55.4	88.3	76.7	50.5	21
5	Mean	72	20700	3110000	3120000	0.145	0.0987	0.00470	110
	SD	0.0	4820	1160000	1160000	0.148	0.00699	0.00161	8.1
	CV%	0.0	23.3	37.2	37.3	102	7.08	34.4	7.4
50	Mean	72	166000	33700000	33700000	0.0183	0.0722	0.00398	150
	SD	0.0	33400	10400000	10400000	0.0209	0.00915	0.00118	28
	CV%	0.0	20.1	30.9	30.9	115	12.7	29.8	19

A second single dose pharmacokinetic study was conducted in cynomolgus monkeys via SC or IV dosing at doses of 5, 50 and 200 mg/kg brodalumab at a dose volume of 4 mL/kg. Each group consisted of three monkeys.

Dose Group	SC administration (mg/kg)	Cmax (ng/ml)	Tmax (hr)	$\lambda_{1/2}$ (hr)	AUCINF (hr*ng/ml)	Vz/F (ml)	Cl/F (ml/hr)	MRTINF (hr)
5	Mean	48026.68	44.000	31.05 4	5838442.7	94.315	2.156	92.304
	SD	14004.62	30.199	8.346	1111919.57	16.616	0.346	8.382
	CV%	29.2	68.6	26.9	19.0	17.6	16.1	9.1
50	Mean	402189.9	96.000	25.04	109115264.4	39.254	1.241	197.742
	SD	76261.74	41.569	15.73	34769402.94	10.548	0.384	49.358
	CV%	19.0	43.3	62.8	31.9	26.9	30.9	25.0
200	Mean	1499499.4	52.000	61.99	438669130.13	98.643	1.100	259.001
	SD	379425.9	34.641	5.069	52092263.19	14.243	0.088	17.000
	CV%	25.3	66.6	8.2	11.9	14.4	8.0	6.6

5.2 Toxicokinetics

See toxicity study reviews below.

6 General Toxicology

6.1 Single-Dose Toxicity

No single dose toxicity studies were submitted.

6.2 Repeat-Dose Toxicity

The sponsor conducted a 1-month toxicity study of brodalumab using SC and IV dosing in cynomolgus monkeys. Five animals per group were administered 0, 25, 90 or 350 mg/kg/dose brodalumab once weekly for four weeks. Brodalumab was well tolerated at all dose levels. Small areas of crusted skin were observed on the hands and/or foot of two HD females (SC) and one HD female (IV) starting on Day 15. A periorbital scab was observed on Day 29 in one HD female (IV). These skin changes were reversed in recovery animals. Anti-brodalumab antibodies were detected in 18 out of 40

brodalumab-dosed monkeys. The NOAEL for this study was determined to be 350 mg/kg/dose for both SC and IV routes of administration.

Weekly Dose (mg/kg)	0 SC		25 SC		90 SC		350 SC		350 IV	
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M:5	F:5
Toxicokinetics										
Mean AUC _{Tau} (SD) (hr•µg/mL)										
Day 1	BQL		20700 (4140)		70200 (11600)		212000 (59900)		569000 (141000)	
Day 22	BQL		31900 (16700)		103000 (36600)		325000 (126000)		782000 (199000)	
Mean C _{max} (SD) (µg/mL)										
Day 1	BQL		155 (32.9)		522 (112)		1680 (404)		7270 (1860)	
Day 22	BQL		225 (102)		762 (206)		2400 (780)		10100 (2200)	

A 3-month SC toxicity study was conducted in cynomolgus monkeys using doses of 0, 25, 90 and 350 mg/kg/dose brodalumab. Six animals per group were dosed weekly for three months. Scabs and tissue-swelling at the injection site were noted in 3 HD males and 6 HD females starting on Day 64. One HD female was observed with an abscess on the final day of dosing. All skin changes were correlated with adverse microscopic findings (subacute to chronic histiocytic inflammation). At the end of recovery, one HD male was observed with tissue-swelling at the injection site with minimal chronic histiocytic inflammation. Anti-brodalumab antibodies were detected in 14 out of 36 animals. Mildly increased serum globulin concentrations were noted in HD males and females. The NOAEL for this study was determined to be 90 mg/kg/dose.

Dose Level (mg/kg)	Day 1			Day 78			AR
	C _{max} (µg/mL)	T _{max} (hr)	AUC ₀₋₁₆₈ (µg.hr/mL)	C _{max} (µg/mL)	T _{max} (hr)	AUC ₀₋₁₆₈ (µg.hr/mL)	
25 (n=12)	174	72	23400	233	48	34000	1.44
90 (n=12)	613	72	81600	1180	24	159000	1.93
350 (n=12)	2480	72	322000	4100	24	529000	1.65

C_{max} = Maximum concentration after SC administration.

T_{max} = Time at which C_{max} was observed.

AUC₀₋₁₆₈ = Area under the serum concentration-time curve from 0 to 168 hours postdose.

AR = Accumulation ratio calculated as AUC_{0-168, Day 78} / AUC_{0-168, Day 1}.

Study title: 6 Month Subcutaneous Injection Toxicity Study of AMG 827 in Cynomolgus Monkeys with a 6-Month Treatment-Free Phase

Study no.: 107714
 Study report location: 4.2.3.2
 Conducting laboratory and location: (b) (4)
 Date of study initiation: November 21, 2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Brodalumab, X000306 and X000314, 99.8%

Key Study Findings

Cynomolgus monkeys dosed with 0, 10, 25 or 90 mg/kg/dose SC brodalumab weekly for six months were observed with mild skin changes and histopathology (MD and HD), increased neutrophil counts (HD) and decreased albumin/globulin ratios (MD and HD). These changes were at least partially reversible during the six month recovery period. The NOAEL for this study was determined to be 90 mg/kg/dose.

Methods

Doses: 0, 10, 25 and 90 mg/kg/dose
 Frequency of dosing: Weekly
 Route of administration: SC
 Dose volume: 1.29 mL/kg
 Formulation/Vehicle: Brodalumab diluent (10 mM sodium acetate, 9.0% w/v sucrose, and 0.004% w/v polysorbate 20)
 Species/Strain: Cynomolgus monkeys
 Number/Sex/Group: 4/sex/group
 Age: 4.7 to 7.6 years
 Weight: 2.7 to 8.3 kg
 Satellite groups: 2/sex/group in control and HD groups for recovery
 Unique study design: None
 Deviation from study protocol: None

Observations and Results

Mortality

Daily. No mortality was observed.

Clinical Signs

Daily. An increase in areas of red and/or dry skin was observed in MD and HD animals, most occurring after Day 92. These changes gradually resolved during the recovery phase in one HD male and one HD female.

Incidences of Abnormal Skin Observations during the Dosing Phase

Dose Level (mg/kg/dose)	0		10		25		90	
Sex (number/group)	M (6)	F (6)	M (4)	F (4)	M (4)	F (4)	M (6)	F (6)
Clinical Signs								
Red skin, any site	1	2	2	0	2	2	6	3
Red skin, excluding periorbital	0	1	1	0	1	2	3	3
Dry skin, any site	1	0	0	0	2	1	1	2

Body Weights

Weekly. No effects observed.

Feed Consumption

Daily. No effects observed.

Ophthalmoscopy

Predose and Day 178. No effects observed.

ECG

Weeks 1 and 25. No effects observed.

Hematology

Predose and Day 57 and 120. Increased neutrophil counts were observed in HD males and females. Decreased albumin/globulin ratios were observed in MD and HD females. The change in neutrophil counts reversed during recovery; however, the changes in albumin/globulin ratios were reversed in 50% of animals.

Clinical Chemistry

Predose and Day 57 and 120. No effects observed.

Urinalysis

Predose and Day 57 and 120. No effects observed.

Gross Pathology

Days 184 and 352. No effects observed.

Organ Weights

Days 184 and 352. No effects observed.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Days 184 and 352. Brodalumab-related findings were observed in the thoracic and axillary skin, tongue, injection site, and sternum bone marrow. These effects were not observed in recovery animals.

Text Table 2
Test Article-Related Histologic Findings

Site/Diagnosis/Severity	Sex mg/kg/dose	Males				Females			
		0	10	25	90	0	10	25	90
Skin (Thoracic)									
Dermatitis, superficial, lymphocytic									
	Minimal	0/0 ^a	0	2	1/0	0/0	2	3	3/0
	Slight	0/0	0	0	1/0	0/0	0	1	1/0
Acanthosis/Hyperkeratosis									
	Minimal	0/0	0	1	0/0	0/0	1	2	2/0
	Slight	0/0	0	1	2/0	0/0	0	1	1/0
Infiltrate, macrophages/lymphocytes									
	Minimal	0/1	0	0	0/1	0/0	0	0	0/0
Yeast/Bacteria, superficial, increased									
		0/- ^b	0	2	2/-	0/0	0	2	2/-
Skin (axillary)									
Dermatitis, superficial, lymphocytic									
	Minimal	1/1	1	3	0/0	1/0	1	1	3/0
	Slight	0/0	0	1	2/0	0/0	0	2	0/0
Acanthosis/Hyperkeratosis									
	Minimal	1/0	1	3	0/0	0/0	1	0	1/0
	Slight	0/0	0	1	2/0	0/0	0	3	2/0
Yeast/Bacteria, superficial, increased									
		0/-	0	4	2/-	0/0	0	3	0/0
Tongue									
Glossitis, submucosal									
	Minimal	4/2	4	4	1/2	1/2	3	4	4/1
	Slight	0/0	0	0	3/0	0/0	0	0	0/0
Yeast, intracorneal, present									
		0/-	0	1	1/-	0/-	0	1	0/-
Injection Site (Test Article)									
Infiltrate, macrophages/lymphocytes									
	Minimal	0/1	0	0	0/0	0/0	0	0	0/0
Inflammation chronic/active									
	Minimal	2/0	1	2	4/0	0/0	1	2	2/0
	Slight	0/0	1	0	0/0	0/0	1	2	1/0
Yeast/Bacteria, superficial, increased									
		0/-	0	0	0/-	0/-	0	0	0/-
Sternum Bone Marrow									
Myeloid hypercellularity									
	Minimal	3/0	4	4	0/0	4/0	2	3	0/0
	Slight	0/0	0	0	4/0	0/0	0	0	4/0

^a Number of animals affected. N = 4 for dosing phase; N = 2 for treatment-free phase.

^b Stains for yeast/bacteria not done for treatment-free animals.

Special Evaluation

Antibody Analysis: Days 29, 57, 92, 120, 148, 176, 183, 197, 225, 253, 281, 309, 337, and 351. At the end of the dosing phase, anti-brodalumab antibodies were detected in 10 out of 28 animals dosed with brodalumab. At the end of the recovery phase, anti-brodalumab antibodies were detected in all animals.

Anti-KLH IgM and IgG Analysis: On Days 30 and 45 each animal received one dose of KLH (1 mL/animal of 1 mg/mL KLH solution) by SC injection into the interscapular region. Blood samples from Days 1, 37, 40, 52, 55 and 62 were analyzed for anti-KLH IgM titers using ELISA. Blood samples from Days 1, 37, 40, 52, 55, 62, 66, 73 and 80 were analyzed for anti-KLH IgG titers using ELISA. Predose titers were below the limit of detection. Increased anti-KLH IgM titers were noted on Days 55 and 62 in LD and HD animals. Measurable anti-KLH IgG titers were observed in all animals after Day 30. No dose-related effect on the titers was observed.

Sperm Evaluation: Sperm were analyzed at necropsy for motility, count and morphology. No effect on sperm motility, sperm density or sperm morphology was observed.

Toxicokinetics

Predose and 24, 72, 96, 120 and 168 hours postdose on Days 1, 92 and 176. No substantial difference in brodalumab exposure was observed between males and females. Exposure to brodalumab increased dose proportionally from 10 to 90 mg/kg. On Day 1, the median T_{max} occurred between 48 and 84 hours after the first dose. On Days 92 and 176, the median T_{max} occurred at 24 hours.

Sex	Dose, Route (n)	Day 1			Day 92				Day 176			
		t_{max}^a (hr)	C_{max} (µg/mL)	AUC_{0-168} (µg*hr/mL)	t_{max}^a (hr)	C_{max} (µg/mL)	AUC_{0-168} (µg*hr/mL)	AR	t_{max}^a (hr)	C_{max} (µg/mL)	AUC_{0-168} (µg*hr/mL)	AR
Male	10 mg/kg, SC (n=2)	60 (24-96)	56.8 (NA)	7520 (NA)	24 (24-24)	129 (NA)	18000 (NA)	2.41 (NA)	24 (24-24)	168 (NA)	23300 (NA)	3.06 (NA)
	25 mg/kg, SC (n=3)	72 (24-72)	150 (23.3)	20900 (2630)	24 (24-24)	342 (90.4)	45400 (8730)	2.16 (0.214)	24 (24-24)	403 (42.5)	51600 (5250)	2.48 (0.196)
	90 mg/kg, SC (n=3)	24 (24-72)	454 (125)	60900 (15200)	72 (24-120)	799 (163)	117000 (27700)	2.03 (0.698)	24 (24-72)	1280 (381)	175000 (59100)	2.96 (1.05)
Female	10 mg/kg, SC (n=2)	84 (72-96)	41.4 (NA)	5250 (NA)	48 (24-72)	99.6 (NA)	14900 (NA)	2.82 (NA)	48 (24-72)	138 (NA)	20600 (NA)	3.90 (NA)
	25 mg/kg, SC (n=3)	72 (24-72)	159 (41.6)	21900 (6450)	24 (24-24)	237 (56.7)	32900 (9830)	1.54 (0.372)	24 (24-24)	238 (78.6)	29200 (6250)	1.36 (0.131)
	90 mg/kg, SC (n=3)	72 (24-72)	450 (15.0)	58100 (3290)	24 (24-24)	958 (107)	119000 (8960)	2.05 (0.0524)	24 (24-24)	1250 (202)	145000 (21200)	2.50 (0.408)
Overall	10 mg/kg, SC (n=4)	84 (24-96)	49.1 (16.8)	6380 (2130)	24 (24-72)	114 (44.3)	16400 (5890)	2.61 (0.809)	24 (24-72)	153 (56.5)	21900 (8020)	3.48 (1.04)
	25 mg/kg, SC (n=6)	72 (24-72)	155 (30.5)	21400 (4440)	24 (24-24)	290 (88.7)	39100 (10800)	1.85 (0.436)	24 (24-24)	321 (106)	40400 (13300)	1.92 (0.632)
	90 mg/kg, SC (n=6)	48 (24-72)	452 (79.3)	59500 (9950)	24 (24-120)	879 (151)	118000 (18400)	2.04 (0.443)	24 (24-72)	1270 (273)	160000 (43000)	2.73 (0.759)

C_{max} : maximum observed concentration after subcutaneous (SC) injection

t_{max} : time at observed maximum concentration

AUC_{0-168} : area under the concentration-time curve from 0 to 168 hours

AR: $AUC_{0-168, Day 92 \text{ or } 176} / AUC_{0-168, Day 1}$

NA: Not applicable

C_{max} , AUC_{0-168} , and AR were reported as mean (SD) values. If $n \leq 2$, NA was displayed for SD.

^a t_{max} was reported as a median (min-max) value.

All values were rounded to 3 significant figures after calculations were performed, except t_{max} , which was presented as nominal time.

Dosing Solution Analysis

Days 1 and 183 (Main Phase) and Days 197, 225, 253, 281, 309, 337, and 351 (Recovery Phase). On Day 1, the mean homogeneity values ranged from 95.1% to 97.2% of nominal concentrations. On Days 1, 64 and 183, the mean values for the concentration verification analyses for all test article groups ranged between 95.2% and 107% of nominal concentrations. Brodalumab was not detected in control article formulations.

7 Genetic Toxicology

Based on ICH S6 (Guideline for the Safety Evaluation of Biotechnology-Derived Pharmaceuticals) guidelines, no genetic toxicology studies were conducted with brodalumab.

8 Carcinogenicity

No carcinogenic concerns exist related to the structure or metabolism of brodalumab. As a monoclonal antibody, brodalumab, a large protein, would not be expected to be able to enter the nucleus and interact with DNA. It will be catabolized to peptides and constituent amino acids via normal metabolic pathways.

The sponsor submitted literature reports to assess the carcinogenic potential of brodalumab, an IL-17RA antagonist. The role of IL-17 in angiogenesis, tumor promotion and human carcinogenicity is uncertain as the literature is conflicting. There is evidence that Th17 cells and/or IL-17A/IL-17RA may be involved in both pro- and anti-tumorigenic processes, although the majority of data seems to point towards the protumorigenic role. Th17 cells and IL-17A have been implicated in promoting tumor growth in xenografts and syngeneic tumors in mice via promotion of angiogenesis and down-regulation of anti-tumor immunity. With the absence or reduction of IL-17A (using IL-17A^{-/-} mice or treatment with anti-IL-17A antibodies), tumor growth was reduced. This suggests that inhibition of IL-17 signaling by blocking IL-17RA by administration of brodalumab may result in an anti-tumorigenic environment. Other studies have shown that IL-17A and/or Th17 cells can reduce tumor growth by stimulating anti-tumor immunity and reducing angiogenic stimuli. These studies were generally conducted by introducing exogenous IL-17A, either by transfection of tumor cells with IL-17A expression vectors or by adoptive transfer of tumor targeted-Th17 cells, mechanisms which may be less likely to be relevant for the potential impact of brodalumab (which would be reducing IL-17A signaling). From the data already available, it is evident that the impact of blocking IL-17 signaling is likely to be highly dependent on the situation and context. The net effect may depend on the type of tumor, the stage of tumorigenesis, the tumor location, and the immune system status and function, among other variables.

Therefore, it is impossible to know the carcinogenicity risk of brodalumab. Postmarketing surveillance of malignancy report frequency compared to background rates may provide the most accurate determination of cancer risk for brodalumab.

9 Reproductive and Developmental Toxicology

9.2 Embryonic Fetal Development

The sponsor conducted a dose range-finding developmental toxicity study in rabbits. Due to the development of anti-drug antibodies (ADAs) which decreased drug exposure and caused immune complex deposition and injury in the kidneys of treated animals, it was determined that the rabbit was not a suitable species for the evaluation of reproductive and developmental toxicity of brodalumab.

Study title: Maternal, Embryo-Fetal, and Neonatal Toxicity Study of AMG 827 Administered by Subcutaneous Injection to Pregnant Cynomolgus Monkeys with 6-Month Postnatal Evaluation

Study no.: 107716
Study report location: 4.2.3.5.3
Conducting laboratory and location: (b) (4)
Date of study initiation: May 1, 2009
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Brodalumab, 1012707 and 1018484, 99.8%
KLH Lot #: KE134884, KL138962, and LC142942

Key Study Findings

Three groups of 16-19 pregnant cynomolgus monkeys were administered weekly SC injections of brodalumab (0, 25, 90 mg/kg) from gestation day (GD) 20 to parturition to evaluate potential adverse effects of brodalumab on the pregnant female and on development of the infant. No dam died during this study. There were no treatment related effects on neonatal deaths noted in this study. No brodalumab-related malformations were observed in infants. No treatment related effects on morphologic, functional or immunological development in infants were noted in this study. Under the experimental conditions, a NOAEL for embryofetal development and for prenatal and postnatal development was identified as 90 mg/kg/week.

Methods

Doses: 0, 25, and 90 mg/kg/dose
Frequency of dosing: Weekly
Dose volume: 1.3 mL/kg
Route of administration: SC
Formulation/Vehicle: Brodalumab vehicle (10mM sodium acetate, 9.0% sucrose, 0.004% polysorbate 20)
Species/Strain: Cynomolgus monkeys
Number/Sex/Group: 18 (Control), 19 (LD) and 16 (HD)
Study design: Pregnant monkeys were dosed once weekly from GD 20 to parturition. Infants were observed for 6 months postnatally. On BD138 and BD152, infants were immunized with 1 mL of KLH (5 mg/infant).

Observations and Results

Mortality

Daily. No effects observed.

Clinical Signs

Daily. No effects observed.

Body Weight

Weekly. No effects observed.

Feed Consumption

Daily. No effects observed.

Toxicokinetics

Adult Female Sampling Times:

Gestation Day or Postpartum Day	Time Points – Relative to Dosing	Samples Collected ^a
GD20-GD22	Predose	TK, ADA, mCG, and Exploratory Sample
GD21-GD23	24 hours postdose	TK
GD23-GD25	72 hours postdose	TK
GD24-GD26	96 hours postdose	TK
GD25-GD27	120 hours postdose	TK
GD27-GD29	168 hours postdose	TK
GD48-GD50	Predose	TK, ADA
GD97-GD99	Predose	TK, ADA
GD139-141	Predose	TK, ADA
GD140-142	24 hours postdose	TK
GD142-144	72 hours postdose	TK
GD143-145	96 hours postdose	TK
GD144-146	120 hours postdose	TK
GD146-148	168 hours postdose	TK
PPD14	Not applicable	Milk TK, TK
PPD28	Not applicable	Milk TK, TK, ADA
PPD91	Not applicable	Milk TK, TK, ADA
PPD180 ± 2 days	Not applicable	TK and ADA
Day of abortion/pregnancy loss confirmation (including stillbirth)	Not applicable	TK, ADA

^a ADA- anti-drug antibody; TK – toxicokinetics; mCG – monkey chorionic gonadotropin

Infants Sampling Times:

Birth Day	Time Points – Relative to KLH Dosing	Samples Collected ^a
BD14	Not applicable	TK
BD28	Not applicable	Hem, Flow, TK, and ADA
BD91	Not applicable	Hem, Flow, TK
BD138 ± 2 days	Pre-KLH immunization-I	KLH-Ab (IgM and IgG)
BD145 ± 2 days	7 days post KLH immunization-I	KLH-Ab (IgM and IgG)
BD148 ± 2 days	10 days post KLH immunization-I	KLH-Ab (IgM and IgG)
BD152 ± 2 days	14 days post KLH immunization-I (Pre-KLH immunization-II)	KLH-Ab (IgM and IgG)
BD159 ± 2 days	7 days post KLH immunization-II	KLH-Ab (IgM and IgG)
BD166 ± 2 days	14 days post KLH immunization-II	KLH-Ab (IgM and IgG)
BD173 ± 2 days	21 days post KLH immunization-II	KLH-Ab (IgM and IgG)
BD180 ± 2 days	Pre-necropsy (28 days post KLH immunization-II)	Hem, Flow, TK, ADA and KLH-Ab (IgM and IgG)
As applicable	Day of unscheduled necropsy	Hem, Flow, TK, and ADA

^a Flow – flow cytometry; Hem – hematology; TK – toxicokinetic; ADA – anti-drug antibody;
Ig – immunoglobulins; KLH-Ab – KLH antibodies

The toxicokinetic parameters for brodalumab (AMG 827) in pregnant adult females are provided in the following table.

AMG 827 Toxicokinetic Parameter Summary Table for All Animals

Dose (n: 1 st Dose/18 th Dose)		1 st Dose (GD 20-22)			18 th Dose (GD 139-141)			AR
		t _{max}	C _{max}	AUC ₁₆₈	t _{max}	C _{max}	AUC ₁₆₈	
		(hr)	(µg/mL)	(µg•hr/mL)	(hr)	(µg/mL)	(µg•hr/mL)	
25 mg/kg/dose (n = 18/11-12) ^a	Mean	72.0	198	25300	24.0	141	19000	191 ^b
	SD	(24.0-120)	100	10300	(24.0-72.0)	103	13400	631 ^b
90 mg/kg/dose (n = 16/14) ^a	Mean	72.0	645	84600	24.0	634	77500	0.961
	SD	(24.0-96.0)	175	23900	(24.0-72.0)	349	49200	0.491

All values were rounded to 3 significant figures after calculations were performed.

^a The decrease in the number (N) of animals was due to limited measurable concentrations in the profile to calculate AUC or some animals aborting prior to the 18th dose therefore dosing was stopped and no TK samples were collected. Subsequently calculation of AR was not possible.

^b If the AR value of Animal 2519 is excluded, then the mean and SD for AR would be 0.571 and 0.299, respectively.

C_{max}: maximum observed concentration.

t_{max}: time at observed maximum concentration. t_{max} is presented as median (min-max).

AUC₁₆₈: area under the concentration-time curve from 0 to 168 hours postdose.

AR: AUC₁₆₈, 18th Dose/AUC₁₆₈, 1st Dose.

After weekly SC administration for 18 weeks, measurable concentrations of brodalumab in maternal milk were observed only on PPD 14 and only in the HD group.

Concentrations of brodalumab in infant serum were variable and were not detected in all animals. Serum brodalumab concentrations were measurable out to BD14 in LD infants and BD28 in HD infants. The mean concentration of brodalumab on BD14 in LD and HD infants was 14100 ng/ml (measurable in 4/11 infants) and 108000 ng/ml (measurable in 9/9 infants), respectively. Brodalumab levels were only measurable in HD infants on BD28. The mean concentration of brodalumab on BD28 in HD infants was 31100 ng/ml (measurable in 7/9 infants).

Four out of 13 adult LD monkeys had detectable levels of anti-brodalumab neutralizing antibodies. Three out of the 13 LD adult monkeys had decreased serum concentrations

associated with the presence of neutralizing antibodies. For adult HD monkeys, 2/14 had detectable anti-brodalumab neutralizing antibodies. None of the 14 HD adult monkeys had decreased serum concentrations associated with the presence of neutralizing antibodies.

Dosing Solution Analysis

Predose and monthly. LD and HD solutions were within 10% of nominal concentrations at all test times. Homogeneity samples were within acceptable ranges.

Cesarean Section Data:

A total of 11 control, 11 LD, and 13 HD live infants were delivered by natural birth. One LD infant was delivered by C-section. Gestation length was comparable between all groups.

Pregnancy Outcome:

Group No.	No. of Pregnant Females ^a	Dose Level (mg/kg/dose)	No. of Infants (M/F)	No. of Pregnancy Losses (Fetus M/F/U)	Pregnancy Losses		
					Prior to GD50	GD50 to GD99 (Fetus M/F/U)	After GD99 ^b (Fetus M/F/U)
1	18	0 (vehicle)	5/6	3/2/2	2	0	3/2/0
2	19	25	5/7	1/2/4	3	0/0/1	1/2/0
3	16	90	10/3	1/1/1	0	0	1/1/1

M - male; F - female; U - unknown.

^a Includes 2, 3, and 0 females, in Groups 1, 2, and 3, respectively, that were enrolled onto study to replace early pregnancy losses prior to GD50.

^b Pregnancy losses after GD100 include abortions (GD100-139) and stillbirths (\geq GD140).

Fetal losses occurring prior to GD140 were considered abortions and those occurring on or after GD140 were considered stillbirths. The group incidences of embryonic or fetal losses were 7 of 18 (38.9%) in the control group, 7 of 19 (36.8%) in the LD group, and 3 of 16 (18.8%) in the HD group.

Fetal Losses:

Group No.	Dose Level (mg/kg/dose)	Total No. Pregnant Females Enrolled	Gestation Day of Fetal Loss (Adult Female No./Fetus No.)	Overall Percent Loss	Third Trimester Percent Loss
1	0	18	GD32 (1510/NA) GD46 (1508/NA) GD118 (1511/1116) GD129 (1504/1041) GD160 (1518/1186) GD164 (1513/1131) GD166 (1517/1171)	38.9%	27.8%
2	25	19	GD32 (2501/NA) GD32 (2509/NA) GD46 (2511/NA) GD74 (2515/NA) GD136 (2512/2126) GD145 (2505/2051) GD162 (2510/2106)	36.8%	15.8%
3	90	16	GD117 (3505/NA) GD144 (3512/3121) GD146 (3506/3066)	18.8%	18.8%
Group No.	Dose Level (mg/kg/dose)	Total No. Pregnant Females Enrolled	Gestation Day of Fetal Loss (Adult Female No./Fetus No.)	Overall Percent Loss	Third Trimester Percent Loss
Historical Control Data ^a				23.3%	13.7%
Range				(34/146) 6.7 to 29.4	(20/146) 0 to 28.6

NA – Not applicable

^a Based on 8 ePPND studies conducted at the Testing Facility from 2008 to 2010.

During organogenesis (prior to GD50), embryonic losses were: 2 of 18 (11.1%) in the control group, 3 of 19 (15.8%) in the LD group, and 0 of 16 in the HD group. One abortion occurred at GD74 in the LD group. There were 11 third semester (\geq GD100) abortions/stillbirths: 5 controls, and 3 each in the LD and HD groups. The group incidences of third trimester (fetal) losses were 5 of 18 (27.8%), 3 of 19 (15.8%), and 3 of 16 (18.8%) for the control, LD, and HD groups, respectively. The sponsor believes the deaths were attributable to maternal rejection, umbilical septicemia, and premature birth. There does not appear to be a treatment related effect on neonatal death compared to vehicle control.

For stillborn and aborted fetuses, fetal measurements were unremarkable and were considered within the range of normal variation. All placentas were normal and there were no brodalumab-associated differences in the placentas examined, nor any findings to explain the cause of fetal death in any animal. There were no developmental

abnormalities detected in these fetuses, changes in fetal external or visceral evaluations or weight, or changes in fetal measurements that were considered brodalumab-related.

Offspring

No effects on mortality, clinical signs, body weight or feed consumption were observed in infants. No differences between groups were observed in the infant morphometric measurements, neurological assessments, skeletal evaluations, and hematology. Two MD infants were observed with pectus excavatum.

Infant morphometric measurements included crown-rump length, femur length, foot length, horizontal head circumference, biparietal diameter, occipitofrontal diameter, chest circumference and anogenital distance on BD1, BD28, BD56, BD91 and BD180. Neurological assessment included righting reflex, palmar grasp, clasp-grasp, visual following, prone progression, lipsmack orient, oral reflex, eye reflexes, moro reflex, negative geotaxis, buildup evaluated on BD3, BD7 and BD14. Skeletal evaluation occurred on BD 28 via skeletal radiographs.

Infant Immunological Assessment:

No changes in lymphocyte subsets or monocytes were observed using flow cytometry. Alterations in the peripheral blood mononuclear cells of infant cynomolgus monkeys born to females dosed with brodalumab during pregnancy were limited to statistically significant increases in total T cells and Th cells in the LD group at BD91 and BD180 \pm 2 days as compared to the concurrent time-matched control group. No increases in total T cells and Th cells were observed in the HD group. The absolute numbers of circulating total T cells and helper T cells in LD infants were within the range of the historical controls with the exception of 1 infant (2136) which was outside of the range of historical controls for T cells. The sponsor considers these changes to be unrelated to brodalumab exposure.

No brodalumab-related changes were observed in anti-KLH IgM or IgG responses in infants born to female monkeys administered brodalumab in any dose group.

Anti-Drug Antibodies:

24 out of 35 (69%) adult female LD and HD animals were positive for ADAs on at least one time point. Seven out of 24 (29%) immunoassay positive brodalumab-dosed animals also tested positive in the bioassay for the presence of anti-brodalumab neutralizing antibodies. Six out of 21 infants (29%) in the brodalumab-exposed groups tested positive for ADAs; 2 of these animals (33%) tested positive for anti-brodalumab-neutralizing antibodies. The mothers of all anti-brodalumab positive infants tested positive for ADAs. ADAs were detected in the control group. Eight out of 18 (44%) adult females tested positive for ADAs on at least 1 time point during the study, and 1 (13%) tested positive for anti-brodalumab-neutralizing antibodies. Five out of 11 (45%) infants tested positive for ADAs. All 5 immunoassay positive infants were born to ADA positive mothers. The time course and magnitude of the antibody responses are consistent with an immune response. The high occurrence and high assay signal from antibodies to brodalumab in animals in the control group was unexpected by the sponsor and the

cause is unknown. Based on assay validation performed using rabbit anti-AMG 827 polyclonal antibody, brodalumab in the serum at concentrations $\geq 50 \mu\text{g/mL}$ may have interfered with the detection of ADAs in the immunoassay. The sponsor believes that brodalumab in the serum at concentrations $\geq 1.56 \mu\text{g/mL}$ may have interfered with the detection of anti-brodalumab neutralizing antibodies in the bioassay.

10 Special Toxicology Studies

The sponsor conducted a local tolerance study in rabbits to evaluate different concentrations and formulations when administered as a single SC injection. One male NZW rabbit was dosed with each concentration/formulation variation at a volume of 1.0 mL per injection site. Brodalumab at 140 mg/mL was associated with local injection site irritation including edema and erythema. These effects resolved by 72 hours post dosing.

The sponsor conducted a tissue cross-reactivity study in human, monkey and rabbit tissues using 20 $\mu\text{g/mL}$ and 2 $\mu\text{g/mL}$ brodalumab. Brodalumab-specific staining was present in the human, cynomolgus monkey and rabbit tissues in the following sites:

- Cytoplasm and cytoplasmic filaments/granules in intrinsic and/or vascular smooth myocytes and myofibroblasts (all species)
- Cytoplasm and cytoplasmic granules in striated skeletal and cardiac myocytes (cynomolgus monkey and rabbit)
- Membrane, cytoplasm, and cytoplasmic granules in resident and/or migrating mononuclear/dendritic cells in multiple tissues (all species)
- Membrane and cytoplasmic granules in hair follicle epithelial cells (all species)
- Basement membrane of epidermis and mucosal epithelium in several tissues (all species)

11 Integrated Summary and Safety Evaluation

In the pivotal repeat dose cynomolgus monkey toxicity study, animals dosed with 0, 10, 25 or 90 mg/kg/dose SC brodalumab weekly for six months were observed with mild skin changes and histopathology (MD and HD), increased neutrophil counts (HD) and decreased albumin/globulin ratios (MD and HD). These changes were at least partially reversible during the recovery period. The NOAEL for this study was determined to be 90 mg/kg/dose.

Three groups of 16-19 pregnant cynomolgus monkeys were administered weekly SC injections of brodalumab (0, 25, 90 mg/kg) from GD 20 to parturition to evaluate potential adverse effects of brodalumab on the pregnant female and on development of the infant. No dam died during this study, and no brodalumab-related abnormalities were observed in infants. However, maternal brodalumab treatment was associated with neonatal deaths (25, 90 mg/kg) and maternal neglect (90 mg/kg). Under the experimental conditions, a NOAEL for prenatal and postnatal development could not be determined.

No genetic toxicity or carcinogenicity studies have been conducted with brodalumab. The sponsor conducted a literature review to assess the carcinogenic potential of IL-17RA inhibition, but the literature was not definitive. The majority of the references suggest there is no increased carcinogenic potential from IL-17RA or IL-17 inhibition. No nonclinical studies to assess the carcinogenic potential of brodalumab were/are recommended.

SILIQ is approvable for the treatment of moderate-to-severe plaque psoriasis from a pharmacology/toxicology perspective.

12 Appendix/Attachments

Appendix #1 Multiples of human exposure calculations based on a mg/kg comparison

Maximum recommended human dose is 3.5 mg/kg ($210 \text{ mg} \div 60 \text{ kg} = 3.5 \text{ mg/kg}$).

NOAEL in the ePPD monkey study is 90 mg/kg. The multiple of human dose for the ePPD monkey study is 26 ($90 \text{ mg/kg} \div 3.5 \text{ mg/kg} = 26$).

Appendix #2 Clean version of recommended label

(Note: Sections 8.3 and 13.2 were deleted as they are unnecessary)

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

SILIQ™ is a human interleukin-17 Receptor A (IL-17RA) antagonist indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no (b) (4) data on SILIQ use in pregnant women. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of brodalumab during organogenesis through parturition at doses up to 26 times the maximum recommended human dose (MRHD) [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

A combined embryofetal development and pre- and post-natal development study was conducted in cynomolgus monkeys administered brodalumab. No brodalumab-related effects on embryofetal toxicity or malformations, or on morphological, functional or immunological development were observed in infants from pregnant monkeys administered weekly subcutaneous doses of brodalumab up to 26 times the MRHD from the beginning of organogenesis to parturition (on a mg/kg basis of 90 mg/kg/week).

8.2 Lactation

Risk Summary

There are no data on the presence of brodalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SILIQ and any potential adverse effects on the breastfed infant from SILIQ or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brodalumab is a human monoclonal IgG2 antibody that selectively binds to human IL-17RA and inhibits its interactions with cytokines IL-17A, IL-17F, IL17C, IL-17A/F heterodimer and IL-25. IL-17RA is a protein expressed on the cell surface and is a required component of receptor complexes utilized by multiple IL-17 family cytokines. Blocking IL-17RA inhibits IL-17 cytokine-induced responses including the release of proinflammatory cytokines and chemokines.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of SILIQ. Published literature is mixed on the potential effects on malignancy risk due to the inhibition of the IL-17RA, the pharmacological action of SILIQ. Some published literature suggests that IL-17A directly promotes cancer cell invasion which suggests a potential beneficial effect of SILIQ. However, other reports indicated IL-17A promotes T-cell mediated tumor rejection which suggests a potential adverse effect by SILIQ. However, inhibition of the IL-17RA with SILIQ has not been studied in these models. Therefore, the relevance of experimental findings in these models for malignancy risk in humans is unknown.

In cynomolgus monkeys, there were no effects on fertility parameters such as reproductive organs or sperm analysis following subcutaneous administration of brodalumab at dose levels up to 90 mg/kg/week for six months (26 times the MRHD on

a mg/kg basis). The monkeys were not mated in this study to evaluate effects on fertility.

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/s/

CARMEN D BOOKER
07/11/2016

BARBARA A HILL
07/12/2016

Comments on BLA 761032

From A. Jacobs

May 9, 2016

1. I concur that there are no pharm-tox approval issues
2. I have conveyed other comments to the reviewer, and she will address them as appropriate

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

/s/

ABIGAIL C JACOBS
05/09/2016