CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125504Orig1s000

PHARMACOLOGY REVIEW(S)
Pharmacology/Toxicology Supervisory Memorandum

BLA number: 125504
SDN/date/type of submission: 21 / October 24, 2013/ New BLA
Applicant: Novartis Pharmaceuticals Corp
Supervisor name: Barbara Hill
Division name: Division of Dermatology and Dental Products
Date: August 7, 2014
Drug: Cosentyx (secukinumab)
Drug class: Human interleukin-17A antagonist
Indication: Psoriasis

General comments:

- I concur with the conclusions contained in Dr. Jill Merrill’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 with the suggested nonclinical labeling changes proposed by Dr. Merrill for this biologic product contained in section 1.3.3 of her review including that the appropriate Pregnancy Category is B.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA A HILL
08/07/2014
Application number: 125504
Supporting document/s: 0
Applicant’s letter date: October 22, 2013
CDER stamp date: October 24, 2013
Product: COSENTYX™ (AIN457, secukinumab)
Indication: moderate to severe plaque psoriasis in adult
patients who are candidates for systemic
therapy or phototherapy
Applicant: Novartis Pharmaceuticals Corp
Review Division: DDDP
Reviewer: Jill Merrill, PhD
Supervisor/Team Leader: Barbara Hill, PhD
Acting Division Director: Kendall Marcus, MD
Project Manager: Matthew White

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction
Secukinumab (AIN457) is a fully human monoclonal antibody directed against the soluble pro-inflammatory cytokine interleukin-17A (IL-17A; also known as IL-17). In humans, IL-17A mRNA and/or protein is upregulated in several inflammatory and autoimmune conditions, including plaque psoriasis. Secukinumab binds to IL-17A, thereby inhibiting its interaction with the IL-17 receptor. Preventing the cytokine/receptor interaction, neutralizes the bioactivity of IL-17A and inhibits the subsequent release of proinflammatory cytokines, chemokines, and mediators of tissue damage. The sponsor anticipates that subcutaneous treatment with secukinumab will clinically reduce the erythema, induration, and desquamation present in plaque psoriasis lesions.

1.2 Brief Discussion of Nonclinical Findings
Secukinumab crossreacts with cynomolgus, rhesus and marmoset monkey IL-17A, but not with rodent IL-17A, making the cynomolgus monkey the most appropriate nonclinical species. Single-dose and repeat-dose toxicity and embryofetal development studies have been conducted with the cynomolgus monkey. A murine surrogate antibody against mouse IL-17A (BZN035) was developed and used for fertility and early embryonic development and peri- and postnatal development studies in mice. Repeat-dose toxicity studies in monkeys (0, 15, 50, 150 mg/kg/week) indicated secukinumab was well tolerated at the injection site with no treatment-related pathology changes during the 26-week treatment and 13-week recovery period. Due to clinical chemistry effects and immunotoxicity (decreases in total lymphocytes, B cells and T cells) observed at the high dose, the NOAEL appears to be 50 mg/kg/week. Clinical dosing at 1/10th the NOAEL (300 mg/60 kg = 5 mg/kg) did not significantly decrease total lymphocytes.

1.3 Recommendations

1.3.1 Approvability
BLA 125504 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 COSENTYX label text. A clean copy of these revised labeling sections is provided in the Appendix as Attachment #2.
HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
COSENTYX is a human interleukin-17A antagonist indicated for the treatment of 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
Pregnancy Category B

There are no adequate and well controlled studies of COSENTYX in pregnant women. Developmental toxicity studies conducted with monkeys found no evidence of harm to the fetus due to secukinumab. COSENTYX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryo-fetal development study was performed in cynomolgus monkeys with secukinumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys that were administered secukinumab weekly by the subcutaneous route during the period of organogenesis at doses up to 30 times the maximum recommended human dose (MRHD; on a mg/kg basis at a maternal dose of 150 mg/kg).

A pre- and post-natal development toxicity study was performed in mice with a murine analog of secukinumab. No treatment related effects on functional, morphological or immunological development were observed in fetuses from pregnant mice that were administered the murine analog of secukinumab on gestation days 6, 11 and 17 and on postpartum days 4, 10 and 16 at doses up to 150 mg/kg/dose.

CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Secukinumab is a human IgG1 monoclonal antibody that selectively binds to interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.
NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of COSENTYX. Some published literature suggests that IL-17A directly promotes cancer cell invasion in vitro, whereas other reports indicate IL-17A promotes T-cell mediated tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male and female mice that were administered a murine analog of secukinumab at subcutaneous doses up to 150 mg/kg once weekly prior to and during the mating period.

2 Drug Information

2.1 Drug

CAS Registry Number

1229022-83-6
875356-43-7
875356-44-8

Generic Name

NA
Code Name

AIN457

Chemical Name

Secukinumab

Molecular Formula/Molecular Weight

$C_{6854}H_{10134}N_{1754}O_{2042}S_{44}$ / 147.9 kDa

Biochemical Description

AIN457 is an IgG antibody and consists of

Pharmacologic Class

Fully human monoclonal antibody that binds and neutralizes IL-17A

### 2.2 Relevant INDs, BLAs and DMFs

IND 100418 (DDDP) for psoriasis

### 2.3 Drug Formulation

Composition of one vial of lyophilized AIN457 150 mg powder solution:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Theoretical amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIN457</td>
<td>150.00</td>
</tr>
<tr>
<td>Sucrose, NF</td>
<td>92.43</td>
</tr>
<tr>
<td>L-Histidine, USP</td>
<td>4.66</td>
</tr>
<tr>
<td>Polysorbate 80, NF</td>
<td>0.60</td>
</tr>
</tbody>
</table>

### 2.4 Comments on Novel Excipients

None
2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Secukinumab is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic or phototherapy. The recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

2.7 Regulatory Background

- 5/27/09: Guidance meeting
- 7/15/09: Guidance meeting
- 3/2/11: Guidance meeting
- 4/17/13: Guidance meeting
- 7/24/13: PreBLA meeting

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Binding affinities of secukinumab (AIN457) to human and cynomolgus monkey IL-17A, IL-17A/F and IL-17F as determined by surface plasmon resonance (RD-2012-00620)

Inhibition of IL-6 release from human synoviocytes stimulated with TNF in combination with IL-17A, IL-17 A/F or IL-17 F by secukinumab (AIN457) (RD-2013-00026)

Characterization of the pH-dependent binding of secukinumab (AIN457) to human and cyno FcRn using surface plasmon resonance (RD-2013-00072)

X-ray analysis of the secukinumab Fv complex with human IL-17A: structural insights into selectivity and cross-reactivity (RD-2013-00118)

Cross reactivity of secukinumab with IL-17 family members and other cytokines using surface plasmon resonance (RD-2013-00135)

In vitro functional neutralization of cynomolgus IL-17A and IL-17F by secukinumab (AIN457) (RD-2013-00148).
Inhibition of human IL-17A-IL-17RA interaction by secukinumab (RD-2013-00196)

**Toxicology**

AIN457: A single dose subcutaneous injection toxicity study in the cynomolgus monkey with a 7- and 28-day observation period: Final report amendment no. 1 (Study # 0870084-01)

AIN457: A 4-week intravenous injection (once weekly) toxicity study (including toxicokinetics) in cynomolgus monkey with a 10-week recovery period (study # 070204-03)

AIN457: A 26-week intravenous injection (once weekly) toxicity study in the cynomolgus monkey with a 13-week recovery period (study # 502618-02)

**Special**

Neutralization of IL-17 and of IL-12/IL-23 p40 on host resistance in an acute tuberculosis aerosol infection model (RD-2010-00463)

Experimental analysis of acute murine oral candidiasis after in vivo treatment with neutralizing anti-IL-17A or anti-IL-17F antibodies (Novartis study # 1270309)

Effect of neutralizing IL-17A and IL-17F antibodies on host resistance to acute *Mycobacterium tuberculosis* infection in mice in comparison with neutralizing TNF-α treatment (study # 1280723)

### 3.2 Studies Not Reviewed

The nonclinical studies listed in this section have been previously reviewed (refer to the reviews identified in Section 3.3). A summary of the pivotal information from these nonclinical studies is provided in this document in the corresponding sections. If additional information is required, then refer to the reviews identified in Section 3.3 for more detail.

**Pharmacology**

NVP-AIN457-NX Generation and selection of a human anti-huIL-17 monoclonal antibody (study # RD-2002-01987)

Il-17 receptors A and C are expressed in the human chondrocyte cell line C-20/A4 (study # RD-2010-00142)
NVP-BZN035: a murine anti-mouse IL-17A monoclonal antibody: affinity, crossreactivity and neutralizing activity in vitro (study # RD-2010-00373)

NVP-BZN035 shows dose-related inhibition of knee swelling in mouse antigen-induced arthritis (study # RD-2010-00416)

Cross-reactivity study of biotinylated AIN457 with normal human and cynomolgus monkey tissues (study # IM1508)

Large-scale expression, purification and assessment of biological activity of recombinant IL-17 from cynomolagus, rhesus and marmoset monkey (Study # RD-2004-01178)

Affinity studies of biotinylated NVP-AIN457 and cytokine cross-reactivity using BIAcore (Study # RD-2005-01595)

Anti-human IL-17 monoclonal antibody (external collaboration report, University Medical Center Nijmegen) (Study # RD-2004-01347)

NVP-AIN457-NX-1 blocks human IL-17-induced neutrophil migration in the mouse air pouch model (Study # RD-2004-01063)

**Safety Pharmacology**

Cross-reactivity study of AIN457 with normal human and cynomolgus monkey tissues (Study # IM1115)

NVP-AIN457: antibody-dependent cellular cytotoxicity analysis in vitro (Study # RD-2005-00898)

NVP-AIN457-NX-1: hemolytic potential and blood compatibility (Study # RD-2005-00699)

AIN457: A cardiovascular, CNS, and respiratory safety pharmacology study in cynomolgus monkeys (Study # 690944)

**Pharmacokinetics**

Quantitative determination of AIN457 surrogate (BZN035) in mouse serum by a competitive ELISA: Method description and validation (Study # RS599323)
Determination of anti-AIN457 antibodies in cynomolgus monkey serum by a BIAcore binding assay: Method description and validation (Study # NBx RS562201)

Determination of anti-BZN035 antibodies in mouse serum by ELISA: Method description and validation (Study # NBx RS586091)

Quantitative determination of AIN457 in marmoset monkey serum by a competitive ELISA: method description and validation (Study # BMD R0550671)

Quantitative determination of AIN457 in cynomolgus monkey serum by a competitive ELISA: method description and validation (Study # BMD R0550671-01)

Pharmacokinetics and bioavailability of AIN457 (from CHO cell) following an intravenous or subcutaneous dose in the cynomolgus monkey (Study # DMPK R0600743-1)

Pharmacokinetics of AIN457 (CHO and cells) following an intravenous dose in the cynomolgus monkey: sample analysis with two analytical methods (Study # DMPK R0800115)

Pharmacokinetic study of AIN457 following intravenous dose of two materials and CHO in the monkey: determination of anti-AIN457 antibodies in serum (Study # NBx R0800115-01)

Pharmacokinetic study of AIN457 following an intravenous dose in the marmoset (Study # DMPK R0500186)

AIN457: A 4-week intravenous injection (once weekly) toxicity study in the cynomolgus monkey with a 10-week recovery period: Final report amendment no. 1 (Study # 502617)

Quantitative determination of AIN457 in cynomolgus monkey serum by a competitive ELISA: method description and validation (Study # BMD R0450253)

Quantitative determination of AIN457 in cynomolgus monkey serum by a competitive ELISA (optimized assay procedure): method description and validation (Study # BMD R0450253-01)

Quantitative determination of IL-17 in cynomolgus monkey serum by sandwich ELISA: method description and validation (Study # BMD R0450379)

Quantitative determination of total IL-17 by ELISA in cynomolgus monkey serum from animals treated with AIN457: method description (Study # BMD R0450379-01)
Quantitative determination of total IL-17 by ELISA in cynomolgus monkey serum from animals treated with high doses of AIN457: method description (study # BMD R0450379-02)

Pharmacokinetic study of AIN457 following an intravenous or subcutaneous dose in monkey (study # DMPK P0400373)

Pharmacokinetic study of AIN457 following an intravenous or subcutaneous dose in monkey: determination of formation of anti-AIN457 antibodies in serum (study # BMD 0550037)

**Toxicology**

A 4-week intravenous bolus toxicity study of AIN457 (with an 8-week recovery) in cynomolgus monkey: determination of the formation of anti-AIN457 antibodies in serum (study # 0480179)

AIN457: A 13-week subcutaneous injection (once weekly) toxicity study in the cynomolgus monkey with a 13-week recovery period (study # 502774)

**Reproductive and Developmental Toxicity**

AIN457 surrogate (BZN035): A once weekly subcutaneous injection fertility study in the mouse (study # 901834)

A subcutaneous embryo-fetal development toxicity study in cynomolgus monkey (study # 1939-024)

AIN457 surrogate (BZN035): A subcutaneous injection pre and postnatal study in the mouse with dose administration on gestation days 6, 11, and 17, and on postpartum days 4, 10 and 16 (study # 901835)

**3.3 Previous Reviews Referenced**

IND 100418 reviewed by Dr Barbara Hill (entered in DARRTS 3-29-2012)

IND 100418 reviewed by Dr Carmen Booker (entered in DARRTS 2-04-2010)
4 Pharmacology

4.1 Primary Pharmacology

Secukinumab is a fully human monoclonal IgG1/k antibody that binds to human IL-17A.

A1N457 binds to human recombinant IL-17A with high affinity ($K_D \sim 200$ pM), and crossreacts with cynomolagus, rhesus, and marmoset monkey IL-17A with lower affinity. The dissociation binding constants are shown in the sponsor's table below (taken directly from Section 2.6.2 Pharmacology Written Summary):

<table>
<thead>
<tr>
<th>Data source</th>
<th>Apparent $K_D$ (nM)</th>
<th>Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>[RD-2004-01490]</td>
<td>0.23 ± 0.03</td>
<td>0.37 ± 0.12</td>
</tr>
<tr>
<td>[RD-2005-01595]</td>
<td>6.0 ± 0.7</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>[RD-2012-00620]</td>
<td>9 ± 1</td>
<td>8.8 ± 1.6</td>
</tr>
<tr>
<td>Marmoset</td>
<td>1.2 ± 0.1</td>
<td>1.9 ± 0.3</td>
</tr>
</tbody>
</table>

The lower apparent $K_D$ values for human and cynomolagus monkey IL-17A reported for study # RD-2012-00620 are likely explained by the use of different recombinant IL-17A constructs.

A1N457 does not bind to rodent IL-17A. A multiple sequence analysis of human, rat and mouse IL-17A reveals a lower level of conservation of the secukinumab epitope in rodent IL-17A. All critical epitopes are conserved, with the notable exception of Pro149 (Table 3-7, taken directly from the study report RD-2013-00118). Pro149 is located at the core of the antibody-cytokine interface and this Proline to Serine change in mouse and rat IL-17A is thought to be the most detrimental change affecting secukinumab
recognition. The difference in affinity between human and monkey IL-17A is likely explained by the Asn101 mutation to either lysine (in rhesus and cynomolgus IL-17A) or aspartic acid (in marmoset IL-17A).

Although these differences contribute to the lower affinity of the cynomolgus monkey, it remains the most relevant nonclinical species.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Amino-acid sequence of the epitope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human IL-17A</td>
<td>SSDYYNR L NADGNDYHMNSV VTPIVHH</td>
</tr>
<tr>
<td>Cyco IL-17A</td>
<td>SDDYYNR L KADGNDYHMNSV VTPIVHH</td>
</tr>
<tr>
<td>Rhesus IL-17A</td>
<td>SDDYYNR L KADGNDYHMNSV VTPIVHH</td>
</tr>
<tr>
<td>Marmoset IL-17A</td>
<td>ASDYYNR L DADGNDYHNNSV VTPIVHH</td>
</tr>
<tr>
<td>Mouse IL-17A</td>
<td>PSYLN R Q NAEKLDHHNSV VASIVRQ</td>
</tr>
<tr>
<td>Rat IL-17A</td>
<td>PSYLN R Q NAEKLDHHNSV VSSIVRH</td>
</tr>
</tbody>
</table>

Within the human IL-17 family (IL-17A through IL-17F) IL-17A and IL-17F share the highest amino acid sequence homology (50%), whereas IL-17E (also called IL-25) is the most divergent with only 17% homology to IL-17A. The binding of secukinumab to all human IL-17 family members was assessed by surface plasmon resonance technology (Biacore™) and no binding to IL-17B through IL-17E was detected. Nor does it bind to the unrelated human cytokines IFNγ, IL-1ß, IL-2, IL-6, IL-8, IL-13, IL-18, IL-19, IL-20, IL-22, IL-23, TGFβ1, TGFβ2 and TNFa (RD-2013-00135).

Both human and cynomolgus monkey IL-17A can induce the production of human IL-6 from cultured primary human dermal fibroblasts. The magnitude of IL-6 secretion correlates with the concentration of IL-17A and neutralization of IL-17A leads to reduced IL-6 production from cultured fibroblasts. The data shown in Table 2-8 (taken directly from section 2.6.2 of the submission) were obtained using two different batches of secukinumab, one derived from the original cell line and the other from a different cell line. Secukinumab was able to neutralize the release of IL-6 when the cells were stimulated with either recombinant human or recombinant...
cynomolgus monkey IL-17A. The observed difference in relative potency for human and monkey IL-17A may be explained by the lower affinity of secukinumab for monkey IL-17A.

<table>
<thead>
<tr>
<th>Species origin of IL-17A</th>
<th>Batch E10906.71 (hybridoma)</th>
<th>Batch KB03363A (Sp2/0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>0.372</td>
<td>0.403</td>
</tr>
<tr>
<td>Rhesus monkey</td>
<td>44.763</td>
<td>51.989</td>
</tr>
<tr>
<td>Cynomolgus monkey</td>
<td>66.660</td>
<td>66.747</td>
</tr>
</tbody>
</table>

Human dermal fibroblasts were stimulated with recombinant human or recombinant cynomolgus monkey IL-17A (0.67 nM) [RD-2004-01178-Table 3-1].

Secukinumab at picomolar concentrations potently inhibited the IL-6 release from human synoviocytes when induced by IL-17A (30 pM)/TNFα costimulation with an IC₅₀ value of 0.14 ±0.02 nM. The antibody neutralized the heterodimeric IL-17A/F (1 nM)/TNFα-induced effects at nanomolar concentrations with an IC₅₀ value of 3.30±0.20 nM. In contrast, there was only a weak neutralizing activity of secukinumab on IL-6 release induced by IL-17F (33 nM)/TNFα which was only observed at micromolar concentrations of secukinumab (IC₅₀ value of 1.80±0.17 µM). IL-17F is the weakest of the different IL-17 cytokines used, both in terms of efficacy and potency. Correspondingly, the neutralization by secukinumab was ~13×10³ fold weaker for IL-17F than for IL-17A-costimulated effects in this experimental model (RD-2013-00026).

Secukinumab neutralized IL-6 secretion by primary cynomolgus synoviocytes stimulated with cynomolgus IL-17A or IL-17F in a concentration-dependent manner with complete inhibition observed at secukinumab concentrations equal to or higher than 10 µM (RD-2013-00148).

4.2 Secondary Pharmacology

The neonatal Fc receptor for IgG (FcRn) mediates bidirectional transport and membrane recycling of IgG in epithelial cells. pH-Dependent binding to FcRn is required for maintaining the long serum half-life seen for IgG antibodies in vivo. IgGs and serum proteins, such as albumin, are pinocytosed nonspecifically by the cell and incorporated into the acidic endosome (see Figure a below, taken directly from Roopenian and Akilesh, 2007).
In the low pH environment, IgGs bind to FcRn and are transported back to the cell surface, whereas non-receptor bound proteins are degraded in the lysosome. At physiological pH, the affinity of IgGs to FcRn decreases and IgGs are released from FcRn back into the bloodstream. The same recycling mechanism protects albumin from lysosomal degradation.

The binding of secukinumab to human and cynomolgus monkey FcRn was evaluated using surface plasmon resonance (SPR, Biacore). As determined by SPR, Secukinumab binds to recombinant human and cynomolgus monkey FcRn only at pH 6.0 and not at pH 7.4 (RD-2013-00072). The report concludes that although secukinumab met the prerequisite of pH-dependent binding for a normal in vivo half-life, actual clinical half-lives may be influenced by many factors such as non-specific binding, susceptibility to proteolysis, or immunogenicity.

4.3 Safety Pharmacology

A single GLP study that evaluated the neurological, cardiovascular and pulmonary effects of single intravenous doses of secukinumab up to 100 mg/kg was conducted in cynomolgus monkeys and reviewed by Dr. Barbara Hill (IND 100418, entered in DARRTS 1-4-2007). No treatment related effects on any of the neurological, cardiovascular or respiratory parameters were noted in this study. Further details are available under the original review.
Additionally, there were no qualitative or quantitative electrocardiographic or neurological changes attributable to secukinumab administration in all repeated dose toxicity studies.

5 Pharmacokinetics/ADME/Toxicokinetics

The cynomolgus monkey and the mouse were used as experimental models to evaluate the PK/TK of secukinumab and its mouse surrogate BZN035, respectively. Secukinumab exhibited typical IgG kinetics with a limited volume of distribution and a low clearance, an apparent elimination half-life between 11 and 29 days, and an absolute bioavailability > 60% after subcutaneous administration. Exposure to secukinumab was dose proportional within the dose range investigated in cynomolgus monkey.

See previous reviews for IND 100418 for additional detail if needed.

6 General Toxicology

6.1 Single-Dose Toxicity

A single dose subcutaneous cynomolgus monkey toxicity study was conducted with AIN457 derived from CHO cells (0, 15, 150 mg/kg). Parameters evaluated included mortality, body weights, feed consumption, hematology, clinical chemistry, urinalysis, organ weights, and microscopic evaluation of selected tissues at necropsy. Toxicokinetic and IL-17 evaluations were conducted on days 1 to 5, 8, 15, 22, and 29. No treatment-related effects were noted on any of the parameters evaluated in this study at either the 7- or 28-day post dose observation point. AIN457 administration was well tolerated at the subcutaneous injection site. The NOAEL was 150 mg/kg/dose (AUC$_{0-168\ hr}$ = 198000 µg●hr/mL; C$_{max}$ = 1520 µg/mL).

IL-17 started to accumulate after dosing and maximal IL-17 concentrations were generally reached between 72 and 168 hours (see Figure 2-3, taken directly from the amended final study report #0870084-01). Following that, IL-17 concentrations tended to decrease steadily. Although the profiles were quite consistent within each animal, the IL-17 profiles varied considerably between different animals. Based on this variability a gender specific difference with regard to IL-17 secretion was not detected. The apparent terminal half-life for the 150 mg/kg dose group was 16.1 days in males and 11.75 days in females, which is in the range of typical values observed with IgGs. Serum samples for the detection of anti-AIN457 antibodies were not analyzed since the toxicokinetic profiles did not indicate potential immunogenicity.
6.2 Repeat-Dose Toxicity

The following summaries of previously reviewed repeat-dose toxicity studies also contain information subsequently provided in the amendments. For complete reviews, please consult the original IND review.

**Title:** A 4-week intravenous bolus toxicity study of AIN457 (with an 8-week recovery) in the cynomolgus monkey

Administration of AIN457 derived from CHO cells at intravenous doses of 15, 50, or 150 mg/kg/week for 4 weeks followed by a 10-week recovery period was well tolerated in cynomolgus monkeys (IND 100418, 5-28-2009). No treatment related effects on mortality, clinical signs, body weights, neurological, ophthalmological, ECG, hematology, clinical chemistry, urinalysis, organ weights, immunotoxicity parameters, macroscopic or microscopic parameters were noted in this study. The NOAEL was identified as 150 mg/kg/week (combined AUC$_{0-168 \ hr}$ = 723500 µg●hr/mL, combined mean C$_{max}$ = 6960 µg/mL), the highest dose evaluated (study # 0770204-03).
Title: AIN457: A 13 week subcutaneous injection (once weekly) toxicity study in the cynomolgus monkey with a 13-week recovery period. Final report amendment no. 1

In a 13-week toxicology study (study # 0770712-01), AIN457 derived from CHO cells was administered by the subcutaneous route to cynomolgus monkeys at 15, 50, and 150 mg/kg/week (3/sex/group) followed by a 13-week recovery period (2/sex/group). IL-17 levels were variable and often just above the limit of detection and reversed during recovery. The original reviewer, Dr Carmen Booker, identified increased globulin levels in high dose females (+20%) at Week 13 and evidence of immunotoxicity at both the mid- and high-dose (IND 100418, entered in DARRTS 2-4-2010). Based on evidence for immunotoxicity, the NOAEL was determined to be 50 mg/kg/week with an $\text{AUC}_{0-168 \text{ hr}} = 297000 \mu g\cdot \text{hr/mL}$.

Title: AIN457: A 26-week intravenous injection (once weekly) toxicity study in the cynomolgus monkey with a 13-week recovery period. Final report amendment no. 2

In the pivotal cynomolgus monkey study, AIN457 derived from CHO cells was administered intravenously (15, 50, 150 mg/kg/week; 4/sex/group) for 26 weeks followed by a 13-week recovery period (2/sex for control and high dose group only; study # 502618; IND 100418, entered in DARRTS 2-4-2010). AIN457 appeared to cause decreases in CD4+ T lymphocytes and increases in CD16+ lymphocytes at the high dose and decreased NK cell activity at the mid- and high-dose levels. Immunotoxicity was observed in one high-dose female (#451) that developed skin lesions (treated with antibiotics), splenic lymphocytic atrophy, decreased NK cell activity, and decreased T-cell dependent antigen response (TDAR; see below). Based on these data, the NOAEL appears to be 50 mg/kg/week with an $\text{AUC}_{0-168 \text{ hr}}$ of 316000 $\mu g \cdot \text{hr/mL}$. The TDAR analysis as described below did not alter the NOAEL determination for this study.

The TDAR data were not included in the original study report, but were added by amendment (study # 502618-02) and reviewed below:

TDAR

**Methods:** Primary IgM and IgG antibody response to a T-cell dependent antigen, keyhole limpet hemocyanin (KLH), was assessed in serum from animals injected on day 162 (main study) and day 253 (recovery group) with KLH solution (KLH with adjuvant aluminum hydroxide) by subcutaneous injection 3 hours after dosing with the vehicle or test article. Cynomolgus monkeys were given weekly doses of vehicle (n=6/sex) or AIN457 at 15 (n=4/sex), 50 (n=4/sex), and 150 mg/kg (n=6/sex) by intravenous injection. During the main study phase, blood was collected prior to dosing with the vehicle/test article on day 162 and on days 166, 170, 175, and 183 (4, 8, 13, 21 days after KLH administration). Anti-KLH IgM (pre-KLH injection, and at 4, 8, and 13 days post-KLH injection) and anti-KLH IgG (pre-KLH injection and 4, 8, 13, and 21 days post-KLH injection) antibodies were measured using commercially available ELISA kits.

Reference ID: 3606290
Results

The concentration levels of anti-KLH IgM and IgG were not detected in most animals until 8 days after injection with KLH solution. High variability in titers between animals and the low number of animals (n=4 for main study, n=2 for recovery) made it difficult to interpret the results. In many cases the vehicle treated groups had higher average IgM titer compared to AIN457 treated male and female groups, but the trend was not consistent.

Analysis of individual animal data reveals that animal #451 (i.e., high-dose female requiring treatment with antibiotics for skin lesions) had the lowest overall anti-KLH IgG response (Table 2.2 Individual T-cell dependent antibody response (anti-KLH IgG) data, taken directly from the study report). Corresponding control animals had a robust IgG titer of 101.37E3 to 726.66E3 U/mL on days 175 and 183, respectively. Animal #451 had IgG titers of 36.11E3 and 28.04E3 U/mL on days 175 and 183, respectively. Thus it appears that animal #451 had a deficient anti-KLH IgG response. In conjunction with development of skin lesions, decreased NK cell activity, and splenic lymphocytic atrophy, it appears that animal #451 developed test article related immunotoxicity.

Table 2.2 Individual T-cell dependent antibody response (anti-KLH IgG) data

<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Group 1 - Placebo control</th>
<th>Group 2 - AIN457 15 mg/kg/dose</th>
<th>Group 3 - AIN457 50 mg/kg/dose</th>
<th>Group 4 - AIN457 150 mg/kg/dose</th>
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<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal Number</td>
<td>Day 162</td>
<td>Day 168</td>
<td>Day 170</td>
<td>Day 175</td>
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<tr>
<td>102</td>
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Reference ID: 3606290
Table 2.2  Individual T-cell dependent antibody response (anti-KLH IgG) data

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<tr>
<th>Group</th>
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<th>Day 170</th>
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Reference ID: 3606290
Table 2.2  Individual T-cell dependent antibody response (anti-KLH IgG) data

<table>
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<th>Recovery period</th>
<th>Females</th>
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<tbody>
<tr>
<td>Group 1 - Placebo Control</td>
<td>Group 4 - AIN457 150 mg/kg/dose</td>
</tr>
<tr>
<td>Animal Number</td>
<td>Day 253</td>
</tr>
<tr>
<td>1</td>
<td>153</td>
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<td>156</td>
</tr>
<tr>
<td>4</td>
<td>456</td>
</tr>
<tr>
<td></td>
<td>463</td>
</tr>
</tbody>
</table>

IL-17A evaluation

IL-17A analysis was conducted by Sandwich ELISA and added by amendment. No IL-17A was detected in the serum of control group animals. Although IL-17A levels started to be detected in treated animals within 24 hours after the first dose and seemed to increase following subsequent dosing, between animal variability was too high for reporting mean concentrations. Based on the considerable variability between subjects, a gender specific difference with regard to IL-17 secretion and capture could not be determined.

7 Genetic Toxicology

Based on ICH S6 (Guideline for the Safety Evaluation of Biotechnology-Derived Pharmaceuticals) guidelines, no genetic toxicity studies were conducted with AIN457.

8 Carcinogenicity

Although secukinumab cross-reacts with human, marmoset, rhesus and cynomolgus monkey IL-17A, it does not cross-react with rodent IL-17A. Thus a standard 2-year carcinogenicity study is not practical and the sponsor has been advised to assess the clinical carcinogenic risk potential of chronic secukinumab-treatment based on the existing scientific literature.

There are no concerns relating to the oncogenic potential arising from the molecular structure or metabolites of secukinumab. Secukinumab is a monoclonal antibody of the IgG1 isotype comprising The catabolism of such proteins into peptides and constituent amino acids is well defined and does not present a carcinogenic risk. Secukinumab acts by extracellular binding to IL-17A for which there is no evidence of a direct mutagenic effect. Furthermore, secukinumab and/or its antibodies are large proteins molecules and are not expected to gain access to the nucleus. Therefore, they are not expected to affect DNA integrity.
IL-17A is considered a proinflammatory cytokine and there is strong in vivo evidence supporting a role for IL-17A in promoting tumors. An anti-IL-17A protocol, such as secukinumab treatment, may therefore have an anti-tumorigenic effect. IL-17A up-regulates the production of a variety of pro-inflammatory cytokines (Kolls 2008) and pro-angiogenic factors (Takahashi 2005) to promote tumor development (Numasaki 2003, Numasaki 2005). Up-regulation of IL-17A expression has also been reported for a wide range of advanced human tumors (Miyahara 2008, Ciree 2004, Alexandrakis 2006), implicating IL-17A in clinical tumor progression.

Nam et al. (2008) demonstrated that CD8+ splenocytes from tumor-bearing mice expressed elevated levels of IL-17A when compared with naïve mice, and that CD8+ cells could be induced to make IL-17A on addition of TGF-β and IL-6 in vitro. IL-17A suppresses apoptosis of several tumor cell lines in vitro, suggesting that altered T-cell polarization observed in tumor bearing mice has the potential to promote tumorigenesis directly, rather than indirectly through inflammatory sequelae.

IL-17A-induced vascular endothelial growth factor (VEGF) production in colorectal carcinoma cells has been suggested as the mechanism underlying the correlation of IL-17A serum levels with angiogenesis and poor prognosis in patients with colorectal carcinoma (Liu et al., 2011). Other researchers note increased IL-17A and VEGF expression in patients with lung adenocarcinoma and suggest IL-17A might promote angiogenesis in these tumors (Li, 2011). IL-17A is associated with disease progression in multiple myeloma due to its effect on angiogenesis since elevated serum levels of IL-17A correlate with increased levels of VEGF and micro-vascular density in bone marrow (Alexandrakis, 2006; Lemancewicz, 2012).

Matrix metalloproteinases (MMP) such as MMP-9 have been shown to promote carcinogenesis by facilitating enhanced tumor invasion, metastasis (Coussens, 2009) and promotion of angiogenesis (Bergers and Coussens, 2000). IL-17A has been shown to induce an increased production of MMPs (Chabaud, 2000; Jovanovic, 2000, 2001). A direct correlation between IL-17A expression and cancer invasiveness was proposed by Zhu, 2008. Addition of IL-17A to a panel of breast cancer cell lines, markedly and significantly up-regulated invasion activity observed in a matrix gel invasion assay. The exact mechanism of IL-17A-dependent tumor cell invasion remains to be determined. Although invasion activity in the matrix gel assay was dependent on MMP-2, MMP-3, and MMP-9, expression of these MMPs and their inhibitors could not be directly stimulated by IL-17A in these cells. This suggests an association of IL-17A in the induction of MMP expression and MMP-mediated cell invasion in tumors.

A study by Xiao (2009) has demonstrated that depletion of IL-17A with a neutralizing monoclonal antibody decreases the 7,12-dimethylbenz(a)anthracene (DMBA)-induced and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced nascent papilloma development in mice by inhibiting the Th17-associated inflammatory reaction induced by IFN-γ.
Other studies have shown that IL-17A has no effect on tumor development and growth. Muranski (2008) demonstrated that tumor-specific Th17 cells could eradicate large established B16 melanomas in mice; however, the effect was mediated by IFN-γ and not IL-17A. Neutralization of IL-17A and/or IL-23 with mouse monoclonal antibodies had no effect on tumor development in this model.

Conversely, several researchers have observed an anti-tumor effect of IL-17A. Kryzcek et al., (2009) studied the effect of IL-17 on tumor growth in IL-17-deficient mice. MC38, a murine colon cancer cell line, was subcutaneously inoculated into the wild-type and IL-17-deficient mice. The IL-17-deficient mice exhibited an accelerated tumor growth compared with the control mice (P<0.01). They also compared the metastatic potential of MC38 cells by intravenously inoculating cells into wild-type and IL-17-deficient mice and observed more metastatic foci of tumors in the lungs of IL-17-deficient mice (59 ±8) than in control mice (12 ± 5; P=0.01). The effect is accompanied by reduced IFN-γ levels in tumor-infiltrating NK cells and T cells. These data suggest that endogenous IL-17 may play a protective role in tumor immunity. In addition, IL-17 has been shown to inhibit the growth of hematopoietic tumors such as mastocytoma and plasmocytoma by enhancing cytolytic T-lymphocytes (Benchetrit et al., 2002). Although IL-17 has been shown to promote tumor growth by inducing angiogenesis, the same process provides the channel through which the immune cells can invade and inflict an assault on the relatively inaccessible tumor cells at the core of the solid tumor mass (Murugaiyan and Saha, 2009). Thus IL-17-induced angiogenesis might also promote antitumor immunity by being a supply channel for immune cells to reach and attack the inner mass of a solid tumor.

The weight of evidence in the scientific literature is that IL-17A may promote cancer, presumably by immunesuppression/impairment of anti-tumor immune response or responses to tumor-promoting viruses. Thus an anti-IL-17A protocol such as secukinumab treatment would not be expected to promote cancer. In support of this concept, no tumors or histological evidence of pre-neoplastic changes were observed in organs or tissues examined following intravenous administration of secukinumab to monkeys at dose levels up to 150 mg/kg per week for 26 weeks followed by a 13-week recovery period.

The risk of malignancy in patients is a safety concern for immunosuppressive drugs in general. Secukinumab is believed to interrupt signaling and cytokine cascades central to psoriasis pathology, presumably by preventing the IL-17A-receptor interaction and subsequent NK cell activation and CD4+T cell differentiation and activation. Long term use of secukinumab may lead to increased risk of tumor development in psoriasis patients, particularly in those who have been exposed to other therapies which could increase the risk of tumor development, such as UVB, photodynamic therapy, and other immunosuppressive agents. Since secukinumab cannot be tested in a traditional 2-year rodent study to evaluate carcinogenic potential due to its species specific binding, the sponsor will monitor malignancy in psoriasis patients administered secukinumab as a part of a comprehensive Risk Management Plan.
9 Reproductive and Developmental Toxicology

The sponsor has generated a mouse IgG1/k monoclonal antibody (BZN035) with appropriate neutralizing activity and specificity for mouse IL-17A for use as a murine surrogate for AIN457. It has been tested in the fertility and early embryonic development (Section 9.1) and prenatal and postnatal development (Section 9.3) studies summarized below.

9.1 Fertility and Early Embryonic Development

The sponsor has conducted a rodent fertility and early embryonic development study using BZN035 (study # 901834; reviewed by Dr. Barbara Hill, IND 100418, entered in DARRTS 3-29-2012). A summary of the study is provided below:

Weekly subcutaneous doses of 0 (vehicle control), 15, 50 and 150 mg/kg BZN035 (AIN457 surrogate) were administered to male CD-1 mice for 4 weeks before mating, during the mating period and until necropsy and to female CD-1 mice for 2 weeks before mating, during the mating period and on gestation day 6. No treatment related effects on reproductive function, fertility or early embryo-fetal development were noted in this study. The no observed effect level (NOEL) was identified as 150 mg/kg/week under the conditions of this study.

9.2 Embryonic Fetal Development

The sponsor has conducted an embryofetal development study (study # 1939-024) in cynomolgus monkeys which was reviewed by Dr Carmen Booker (IND 100418, entered in DARRTS 2-4-2010). A summary of the study and the reviewer’s conclusion are provided below:

A subcutaneous embryofetal development study was conducted in pregnant cynomolgus monkeys dosed with 15, 50, and 150 mg/kg weekly, from day 20 to 50 of gestation or Day 20 to 90 of gestation. Animals were euthanized at Day 100 after caesarean section.

A dose-related increase in misaligned vertebrae in the tail region was observed in all AIN457-treated groups (6.25% (n=1/16) LD animal, 12.5% (n=2/16) MD animals and 37.5% (n=6/16) HD animals), with a significant increase observed at the highest dose tested, 150 mg/kg/week. Although the sponsor dismisses this finding as a known variation in cynomolgus monkeys the dose-related increase suggests it is treatment-related. Therefore, the NOAEL for maternal toxicity was determined to be 150 mg/kg/week but for fetal toxicity the NOAEL was 50 mg/kg/week.

These conclusions were conveyed to the sponsor during a teleconference (October 19, 2011, ). Novartis responded that their review of the data had concluded that the toxicity was not test article-related and requested time to re-evaluate the study findings and determine the background incidence. FDA agreed to review additional
information, but responded that the finding is dose-related and without further support the Agency considers it related to the drug.

In the Toxicology Written Summary (Section 2.6.6) of the BLA submission the sponsor disputes the dose-dependent claim, noting an incidence of vertebrae (asymmetrically ossified), misaligned in 7.7% (n=1/13) of the control animals (see Table: Summary of Fetal Findings, taken directly from the study report). Thus the incidence of misaligned vertebrae in the animals treated with secukinumab at 15 or 50 mg/kg (6.25%, 12.5%, respectively) was comparable to the occurrence in the control group (7.7%).

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Group 3</th>
<th>Group 4</th>
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</tr>
<tr>
<td>Vertebr(e), not to tail end</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Although the findings could still be considered drug related, the sponsor reports misaligned vertebrae were also found in up to 31.3% of control fetuses in embryo-fetal development studies performed at the same contract research organization ( ). These findings are reproduced below in Table 6-1(taken directly from the BLA submission). The sponsor notes that in historical studies an increased incidence of misaligned vertebrae of up to 41% (Table 6-1, study #1) could be found in studies concluded as negative. Therefore, this observation is classified as a normal spontaneous finding in cynomolgus monkeys and not considered caused by secukinumab administration.
Table 6-1  Incidence of misaligned vertebra(e) in embryo fetal development studies in cynomolgus monkeys at individual study historical data

<table>
<thead>
<tr>
<th>Study</th>
<th>Group 1 (Control)</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>31.25% (n= 5/16)</td>
<td>15.40%</td>
<td>41.20%</td>
<td>21.40%</td>
</tr>
<tr>
<td>Study 2</td>
<td>16.66% (n= 2/12)</td>
<td>15.40%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Study 3</td>
<td>20.00% (n= 3/15)</td>
<td>7.1%</td>
<td>7.1%</td>
<td>14.30%</td>
</tr>
<tr>
<td>Study 4</td>
<td>16.66% (n= 2/12)</td>
<td>20%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

The studies presented in this table were concluded to show no test article related effect and are therefore relevant as "control" data reference.

The sponsor also evaluated skeletal assessment (x-ray) data from 63 monkeys (~3 months of age) from 5 peri- and postnatal studies (historical data reference from ) where such findings were not detected. Since the embryo-fetal data suggests misaligned vertebrae are regularly observed as background in control or treated animals but not in peri- and postnatal development studies with x-ray examination, it is therefore assumed that this finding spontaneously resolves during the postnatal development of the infants.

Reviewer's comment: As further support for no drug-related skeletal effect the sponsor notes that during the peri- and postnatal development study conducted in mice with the murine surrogate antibody BZN035, no treatment-related skeletal findings were noted in the F1 or F2 generation. However, these findings would not have been observed during the peri- and postnatal development study because skeletal examination is not part of the protocol.

The additional historical control data support the sponsor’s assessment that the NOAEL for malformations in the monkey EFD study is 150 mg/kg/week.

9.3  Prenatal and Postnatal Development

The sponsor has conducted a rodent pre- and postnatal development study using BZN035 (study # 901835; reviewed by Dr. Barbara Hill, IND 100418, entered in DARRTS 3-29-2012). A summary of the study is provided below:

Subcutaneous doses of 0 (vehicle), 15, 50 and 150 mg/kg/dose BZN035 (AIN457 surrogate) were administered to pregnant CD-1 mice (F0 generation dams) on gestation days (GD) 6, 11, and 17, and on postpartum days (PPD) 4, 10 and 16. All BZN035 dams and their offspring were exposed to BZN035. No treatment related effects on F0 generation clinical condition, body weight, feed consumption, maternal performance or macroscopic parameters were noted in this study. The no observed adverse effect level (NOAEL) for the F0 generation was identified as 150 mg/kg/dose.

There were no treatment related effects on survival, growth, development, behavior or reproductive performance in the offspring (F1 generation). Treatment related minor changes were noted in the lymphocyte populations in the blood, thymus, and spleen.
These minor changes in lymphocyte populations were not considered significant since there were no treatment related effects on T cell-dependent antibody responses (TDAR) noted in this study. There were no treatment related effects on the F2 generation. The NOAEL for the F1 generation was identified as 150 mg/kg/dose.

10 Special Toxicology Studies

Secukinumab therapy is designed to neutralize critical mediators of innate and adaptive immunity. Thus it may carry the risk of an increased susceptibility to infection. In addition to assessing the infection risk of secukinumab treatment in the repeat dose toxicity studies conducted in cynomolgus monkeys, the sponsor has tested an anti-mouse-IL-17A antibody in investigative studies in mouse models of infection.

Title: Neutralization of IL-17 and of IL-12/IL-23 p40 on host resistance in an acute tuberculosis aerosol infection model

In a 4-week study testing the effect of neutralizing IL-17 and IL-12/IL-23-p40 antibody formation on host resistance, four groups of 10 female mice were exposed to an intranasal infection using *Mycobacterium tuberculosis* H37Rv (1000 colony forming units (CFU; RD-2010- 00463). Seven additional TNF-deficient mice were also exposed to the aerosol infection, serving as a positive control. The intraperitoneal administration of IL-17, IL-12/p40 neutralizing and isotype control antibodies at 1 mg per mouse per week had no significant effect on body weight development, but did have some unexplained effects on relative organ weights. The macroscopic and microscopic investigations at 2 and 4 weeks did not reveal any significant differences in the antibody administered-mice as compared to the saline control. The inflammatory changes were comparable in all groups, and there is no evidence from the microscopic evaluation of the lung that the antibody neutralization enhanced the growth of mycobacteria or inflammatory pathology. The bacterial load in lung was not significantly affected by the administration of the antibodies, except an increase in colony forming units in the lung at 2 weeks, but not 4 weeks of mice receiving IL-12/p40. In contrast, the same infectious inoculum in TNF-deficient mice caused dramatic systemic disease with body weight loss, severe inflammatory lung pathology, extensive necrosis and uncontrolled mycobacterial growth. Data from this study suggest that antibody neutralization of IL-17 or IL-12/p40 has no significant effect on host resistance to acute mycobacterium infection over 4 weeks in mice.

*Reviewer's comment:* The anti-mouse IL-17 antibody was purchased from (b) (4) and has been demonstrated to neutralize IL-6 secretion elicited by recombinant mouse IL-17.

Title: Experimental analysis of acute murine oral candidiasis after in vivo treatment with neutralizing anti-IL-17A or anti-IL-17F antibodies

To examine the potential role of IL-17A neutralization in fungal infection, the sponsor used a murine model of acute oropharyngeal candidiasis (OPC), in which normal mice
clear infection by Day 4 (study # 1270309). Following oral *Candida albicans* exposure, C57BL/6 (wild type) mice were treated with isotype control antibodies or neutralizing anti-IL17A or anti-IL17F antibodies and fungal burden in the tongue and body weight changes were assessed. IL-17A neutralization resulted in delayed clearance of OPC with anti-IL-17A-treated mice failing to clear infection by Day 4, but with clearance observed by Day 7 in contrast to isotype-treated or untreated mice, which cleared infection by Day 4. Anti-IL-17F treatment did not impair OPC clearance. Genetically deficient IL-17A mice (IL17a−/−) fully cleared infection by Day 4 similar to wild type mice.

These results highlight differences between cytokine neutralization in vivo versus constitutive genetic ablation of IL-17A.

**Title:** Effect of neutralizing IL-17A and IL-17F antibodies on host resistance to acute *Mycobacterium tuberculosis* infection in mice in comparison with neutralizing TNFα treatment

The effect of neutralizing IL-17A or IL-17F during acute *M tuberculosis* infection was evaluated in a 4-week aerosol mouse model (study #1280723). *M tuberculosis* (strain H37Rv, 1000 CFU)-infected C57BL/6 mice were treated once per week intraperitoneally with 0.5 mg (~20 mg/kg) of anti-mouse IL-17A or IL-17F antibodies, 0.25 mg (~10 mg/kg) of anti-mouse TNFα antibody, and respective isotype control antibodies, starting one day before infection. Disease symptoms, lung and spleen weight, pulmonary bacterial burden and lung histopathology were assessed at day 28. IL-17A or IL-17F neutralization was similar in effect to the isotype controls and did not alter body, lung, and spleen weights, pulmonary bacterial burden or lung histopathology after 28 days. On the other hand, in mice treated with a neutralizing anti-TNFα antibody, body weight was drastically decreased, while lung inflammation and pulmonary bacterial burden were clearly increased by day 28. These changes were associated with a worsening of the microscopic observations in the lung with the anti-TNFα antibody. TNFα-deficient mice succumbed by day 28 to severe infection under these experimental conditions. These results confirm the importance of TNFs in host resistance to *M tuberculosis* and highlight that anti-IL-17A or anti-IL-17F cytokine neutralization during 4 weeks in vivo does not impair immunity in an acute mouse *M tuberculosis* infection model.

The sponsor has also reviewed the scientific literature to assess IL-17 neutralization and nonclinical infection risk. IL-17 pathway-deficient mice show susceptibility to numerous bacterial and fungal pathogens. In contrast, humans with IL-17 pathway-deficiencies show a more selective susceptibility, in particular to the fungus *C albicans*, and to a lesser extent the bacterium *S aureus*. Notably IL-17A neutralization is not broadly immunosuppressive and there is no evidence for impairment of resistance to *M tuberculosis*. Thus animal models of human infection may overestimate infection risks relevant to man (Cypowyj *et al.*, 2012). von Bernuth *et al.*, (2012) state, “Immunological redundancy is greater in the course of natural infections in outbred human populations than in the course of experimental infections in inbred mice.” Novartis intends to address the infection risk potential of secukinumab in their risk management plan and will continue to monitor this through pharmacovigilance activities.
11 Integrated Summary and Safety Evaluation

In the pivotal cynomolgus monkey study, AIN457 derived from CHO cells was administered intravenously (15, 50, 150 mg/kg/week; 4/sex/group) for 26 weeks followed by a 13-week recovery period (2/sex for control and high dose group only; study # 502618; IND 100418, entered in DARRTS 2-4-2010). Once weekly treatment with secukinumab appeared to cause decreases in CD4+ T lymphocytes and increases in CD16+ lymphocytes at the high dose and decreased NK cell activity at the mid- and high-dose levels. Immunotoxicity was observed in one high-dose female (#451) that developed skin lesions (treated with antibiotics), splenic lymphocytic atrophy, decreased NK cell activity, and decreased T-cell dependent antigen response. Based on these data, the NOAEL appears to be 50 mg/kg/week.

Weekly subcutaneous administration of secukinumab to pregnant cynomolgus monkeys (gestation day 20 to 90) did not elicit maternal toxicity and no embryo-fetal toxicity or malformations was observed in this study. No treatment related effects on fertility or pre- and post-natal development were noted in mice treated with the mouse analog of secukinumab.

No genetic toxicity or carcinogenicity studies have been conducted with secukinumab. The sponsor has conducted a literature review to assess the carcinogenic risk potential of inhibiting IL-17A which correlates to potential effects after treatment with secukinumab. The literature results were not definitive but the majority of the literature references indicate no increased carcinogenic potential after inhibition of IL-17A. In addition, no preneoplastic lesions were noted during the 26-week repeat-dose toxicity study in monkeys. No nonclinical studies to address the carcinogenic potential of secukinumab are recommended.

COSENTYX is approvable for the treatment of severe plaque psoriasis from a pharmacology/toxicology perspective.

12 Appendix/Attachments

Attachments Included in the Appendix

Attachment #1 – References

Attachment #2 – Revised nonclinical sections of the COSENTYX label

Attachment #1 – References


Attachment #2 – Revised nonclinical sections of the COSENTYX label

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

COSENTYX is a human interleukin-17A antagonist indicated for the treatment of 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

Pregnancy Category B

There are no adequate and well controlled studies of COSENTYX in pregnant women. Developmental toxicity studies conducted with monkeys found no evidence of harm to the fetus due to secukinumab. COSENTYX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryofetal development study was performed in cynomolgus monkeys with secukinumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys that were administered secukinumab weekly by the subcutaneous
route during the period of organogenesis at doses up to 30 times the maximum recommended human dose (MRHD; on a mg/kg basis at a maternal dose of 150 mg/kg).

A pre- and post-natal development toxicity study was performed in mice with a murine analog of secukinumab. No treatment related effects on functional, morphological or immunological development were observed in fetuses from pregnant mice that were administered the murine analog of secukinumab on gestation days 6, 11 and 17 and on postpartum days 4, 10 and 16 at doses up to 150 mg/kg/dose.

**CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.

**NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of COSENTYX. Some published literature suggests that IL-17A directly promotes cancer cell invasion in vitro, whereas other reports indicate IL-17A promotes T-cell mediated tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male and female mice that were administered a murine analog of secukinumab at subcutaneous doses up to 150 mg/kg once weekly prior to and during the mating period.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JILL C MERRILL
08/07/2014

BARBARA A HILL
08/07/2014

Reference ID: 3606290
Comments on BLA 125504 Secukinumab

Date: May 14, 2014

From A. Jacobs, AD

1. I concur that there are no pharm-tox approval issues

2. I concur that the pregnancy category is B
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
05/16/2014
On initial overview of the BLA application for filing:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?</td>
<td>Y</td>
<td></td>
<td>Formatted to allow substantive review.</td>
</tr>
<tr>
<td>2 Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?</td>
<td>Y</td>
<td></td>
<td>Indexed and paginated to allow substantive review.</td>
</tr>
<tr>
<td>3 Is the pharmacology/toxicology section legible so that substantive review can begin?</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?</td>
<td>Y</td>
<td></td>
<td>As requested, the sponsor has submitted a nonclinical carcinogenic risk assessment.</td>
</tr>
<tr>
<td>5 If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations?  (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).</td>
<td>Y</td>
<td></td>
<td>The mouse surrogate antibody BZN035 was shown to be a valid biological surrogate for secukinumab and was therefore used to perform a fertility and early embryonic development study and a pre-and postnatal development study.</td>
</tr>
<tr>
<td>6 Does the route of administration used in the animal studies appear to be the same as the intended human exposure route?  If not, has the applicant submitted a rationale to justify the alternative route?</td>
<td>Y</td>
<td></td>
<td>Intended human exposure route is subcutaneous and all nonclinical studies were conducted with parenteral administration.</td>
</tr>
<tr>
<td>7 Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?</td>
<td>Y</td>
<td></td>
<td>Stated on page 9, Nonclinical Overview.</td>
</tr>
<tr>
<td>8 Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57?</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)</td>
<td>Y</td>
<td></td>
<td>No impurity issues were identified under IND 100418.</td>
</tr>
<tr>
<td>11. Has the applicant addressed any abuse potential issues in the submission?</td>
<td></td>
<td></td>
<td>Not applicable.</td>
</tr>
<tr>
<td>12. If this BLA is to support a Rx to OTC switch, have all relevant studies been submitted?</td>
<td></td>
<td></td>
<td>Not applicable.</td>
</tr>
</tbody>
</table>

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 60-day letter.

None.

Jill Merrill 12-2-2013
Reviewing Pharmacologist

Barbara Hill see sign-off date
Team Leader/Supervisor
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JILL C MERRILL
12/02/2013

BARBARA A HILL
12/02/2013