



European Medicines Agency  
*Evaluation of Medicines for Human Use*

Doc.Ref.: EMEA/CHMP/29255/2009

**ASSESSMENT REPORT**

**FOR**

**STELARA**

International Nonproprietary Name: ustekinumab

**Procedure No. EMEA/H/C/000958**

Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted.

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# **1. BACKGROUND INFORMATION ON THE PROCEDURE**

## **1.1 Submission of the dossier**

The applicant Janssen-Cilag International NV submitted on 04 December 2007 an application for Marketing Authorisation to the European Medicines Agency (EMA) for STELARA, through the centralised procedure falling within the Article 3(1) and point 1.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The applicant applied for the following indication: "Treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA".

### **Scientific Advice:**

The applicant received Scientific Advice from the CHMP on 26 May 2005 and 18 October 2006. The Scientific Advice pertained to quality and clinical aspects of the dossier.

### **Licensing status:**

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ian Hudson

Co-Rapporteur: David Lyons

## **1.2 Steps taken for the assessment of the product**

- The application was received by the EMA on 04 December 2007
- The procedure started on 26 December 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2008.
- During the meeting on 21-24 April 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 April 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 July 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 September 2008.
- During the CHMP meeting on 22-25 September 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 October 2008.
- During the meeting on 17-20 November 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to STELARA on 20 November 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 November 2008.

## 2. SCIENTIFIC DISCUSSION

### 2.1 Introduction

Psoriasis is one of the most common human skin diseases and affects 2 to 3% of the general population. It is a complex disorder, characterized by inflammation, increased keratinocyte hyperproliferation, and an altered epidermal differentiation population. Substantial evidence exists indicating that T-lymphocytes, macrophages, and certain cytokines play a major role in the pathogenesis of the disease.

Interleukin (IL)-12 is a heterodimeric cytokine consisting of 2 disulfide-linked glycosylated subunits, designated p35 and p40. The p40 protein subunit of IL-12 can also associate with a 19.8 kilodalton protein, p19, to form a novel cytokine, IL-23. It is thought that IL-12 induces proliferation of naïve T-cell populations, and IL-23 is stimulatory to memory T-cell populations.

IL-12 is produced primarily by antigen presenting cells, which play a key role in promoting Th1 responses. Th1 cells are characterized by their secretion of interferon. Th1 cells also promote both cell-mediated immunity, and the synthesis of complement-fixing antibody isotypes.

Recently, a neutralizing antibody to IL-12 has been found to abolish the formation of psoriaform lesions in a murine model of the disease. IL-12 has been shown to play a role in the pathogenesis of a psoriasis-like skin disorder in severe combined immunodeficiency disorders (SCID) mice.

The present application for marketing authorisation of Stelara is made under Article 8.3 and concerns a new active substance, ustekinumab, for which a complete dossier has been submitted.

The applied indication for STELARA was for the treatment of moderate to severe plaque psoriasis in adults who have had an inadequate response to, or who have a contraindication to, or who are intolerant to systemic therapy (e.g. cyclosporin, methotrexate or psoralen plus ultra-violet A light [PUVA]).

Stelara has been approved in the following restricted indication: “treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA”.

Stelara is presented as a solution for subcutaneous injection and is supplied in glass vials with a stopper and flip-off cap. It is manufactured in two dosages, a 45 mg vial (0.5 mL) and 90 mg vial (1.0 mL).

Stelara is a fully humanised monoclonal antibody composed of an IgG1 heavy chain isotype and a kappa light chain isotype with an approximate molecular weight of 148,600 Daltons. ustekinumab binds with high affinity and specificity to a 40 kilo Dalton (kDa) human protein that is a subunit of both interleukin (IL)-12 and IL-23 heterodimeric cytokines. This subunit is called IL-12/23p40. ustekinumab neutralises IL-12 and IL-23 bioactivity by binding to IL-12/23p40 and preventing IL-12 and IL-23 binding to the IL-12R $\beta$ 1 receptor protein expressed on the surface of natural killer (NK) or T cells. Through this mechanism of action, ustekinumab neutralizes IL-12 (Th1) and IL-23 (Th17) mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with a variety of immune-mediated human diseases, including psoriasis, Crohn’s disease, rheumatoid arthritis, ulcerative colitis and others.

ustekinumab has been studied clinically in patients with chronic moderate to severe plaque psoriasis, psoriatic arthritis, Crohn’s disease and multiple sclerosis. In clinical trials, subjects were given single doses of ustekinumab via intravenous (IV) and subcutaneous (SC) routes of administration at doses up to 4.5 mg/kg and 2.7 mg/kg, respectively. In addition, multiple fixed SC doses of ustekinumab have been administered at doses up to 180 mg per week. The recommended dose of ustekinumab for

psoriasis patients is 45 mg administered SC at weeks 0 and 4, then every 12 weeks thereafter. A dose of 90 mg may be used in patients with a body weight greater than 100 kg.

An application for a marketing authorisation is pending in the United States of America where it was originally submitted in November 2007.

There were two Scientific Advice procedures. The first from February to May 2005 and the second from August to October 2006.

The Applicant's procedures appear compliant with GMP, GLP and GCP. Stelara drug substance is manufactured at Centocor Biologics, LLC 4777 LeBourget Drive St. Louis, MO 63134 USA. Manufacture of Stelara final vial product (FVP) is performed at Cilag AG Hochstrasse 201 8205 Schaffhausen.

Release and stability testing of the ustekinumab FVP is performed at Centocor B.V. Einsteinweg 101 2333 CB Leiden The Netherlands.

The pivotal non-clinical toxicity studies were all reported to be GLP-compliant. Some deviations from GLP have been documented but none is considered to have invalidated any of the studies involved.

Some deviations from GCP (including a serious breach in blinding at one site in the comparator trial with etanercept- affecting one patient in the UK) were noted but were not considered to affect the overall quality of the data as analysis of the data.

## **2.2 Quality aspects**

### **Introduction**

ustekinumab is expressed in Sp2/0 murine myeloma cell line using a protein-free, chemically defined cell culture medium and purified by a series of affinity and ion exchange chromatographic steps and viral inactivation steps.

The drug substance is formulated with L-histidine, sucrose and polysorbate 80 and water for injection.

ustekinumab is presented as a concentrated solution for injection containing 90 mg/ml ustekinumab in two doses, a 45 mg vial (0.5 mL) and 90 mg vial (1.0 mL).

### **Active Substance**

#### *Description of the drug substance*

ustekinumab is a fully humanised IgG1k monoclonal antibody comprised of 1326 aminoacid residues with two identical heavy and light chains linked by covalent disulfide bonds and non-covalent heavy-heavy and heavy-light chain interactions.

ustekinumab contains a single N-linked glycosylation site at the Asp 299 aminoacid residue of each heavy chain. The major source of molecular weight and charge heterogeneity is due to post-translational modifications caused by different glycoforms and partial loss of the C-terminal lysine.

ustekinumab has a total molecular weight of approximately 148,600 Da.

- **Manufacture**

The drug substance is manufactured at Centocor Biologics, LLC, St Louis, Missouri, USA. in accordance to current EU Good Manufacturing practices (GMP), with standard operating procedures in place to describe all procedures and controls.

ustekinumab formulated bulk (FB) is manufactured by continuous perfusion cell culture. After preculture, expansion of the cell culture, ustekinumab is harvested and purified by a combination of affinity and ion exchange chromatography steps and other steps to inactivate or remove potential virus contamination (solvent/detergent [S/D] treatment and virus removal filtration). Final steps of the manufacturing process include the preparation of the ustekinumab pre-formulated bulk (PFB) and FB.

#### *Cell line development*

Sp2/0 host cell were transfected to express ustekinumab. These cells do not synthesize heavy or light chains proteins. The cells were seeded to adapt growth in protein free chemically defined media.

#### *Development genetics*

Splenocytes from mice immunised with human Il-12 and Ag653 mouse myeloma cells were fused to create hybridomas using a standard technology. The hybridoma cell line C340A expressing an anti human Il-12 was identified and subcloned. A library of DNA fragments was prepared from genomic DNA to clone ustekinumab heavy and light chain genes. The bacteriophage from the library were mixed with an E.coli strain and the pure bacteriophage clones of interest were obtained by DNA hybridization.

The DNA inserts were transferred from the bacteriophage vectors to a pSV2gpt-based expression vector suitable for transfection in mouse myeloma cells C463A cells. The transfection was performed by electroporation. After three rounds of subcloning, the line C743B showed better growth and IgG titre and was chosen as the candidate to establish a MCB.

#### *Cell bank system*

A two-tiered cell banking system of Master Cell bank (MCB) and Working Cell Bank (WCB) has been developed and maintained in accordance to GMP and ICH Q5D guidelines.

A MCB was prepared from the development cell bank (DCB). Each WCB is generated from the MCB. Two WCBs are currently available, one serves as a primary source of production and the second as a backup. A new WCB will be generated periodically to ensure continuous supply for manufacturing.

Two vials of the development bank were thawed and the MCB was obtained following culture and sub-culture of cells in suspension in a selective medium. The WCB was prepared from MCB, using the same procedures as the described for the MCB.

Procedures followed in the preparation of MCB and WCB have been appropriately described. An extensive range of tests has been performed for their characterisation, in accordance with ICH guidelines, including purity, identity, presence of retrovirus and endogenous agents as well as potential non-endogenous and adventitious agents.

#### *Preculture and expansion and bioreactor production*

One or more cryovials of C743B WCB are thawed and diluted with chemically defined medium. The preculture is expanded sequentially in a series of culture flasks and culture bags as mechanism to scale up for inoculation of the seed reactor.

The content of the seed reactor is transferred into the production bioreactor. Continuous perfusion is initiated and culture is drawn from the bioreactor into a cell retention system to separate cells from the permeate. The permeate is filtered and collected as harvest in bioprocess containers. The continuous perfusion cell culture continues up to 60 days post-inoculation.

Cell culture conditions and in-process controls are tested during the culture expansion and at the end of the production.

#### *Purification process*

The purification process of the cell harvest consist of the following purification and virus removal/inactivation steps:

- Affinity chromatography
- S/D treatment
- Cation exchange chromatography
- Anion exchange chromatography
- Virus removal filtration
- Concentration by ultrafiltration and diafiltration

The formulated bulk is prepared by addition of polysorbate 80.

In-process controls are performed in many steps during the purification process.

The upstream manufacturing and purification processes and controls in place for the drug substance are described, including description of the elution buffers, exchange buffers, column regeneration and storage conditions. Validation data for the production processes of the drug substance has been provided and the capacity of the process to remove DNA, host cell protein, residual Protein A and cell culture additives has also been suitably validated.

#### *Manufacturing process development and validation*

The commercial bulk drug substance manufacturing process for Stelara was developed over time to yield a process that is robust, consistent and appropriate for commercial manufacturing.

A comprehensive analytical control strategy was employed throughout development in order to monitor effects of process changes. Whenever significant process changes were made, an additional batch of Reference Standard was manufactured and characterized as part of the comparability program for Stelara. A detailed discussion of the data showing process and product comparability throughout development was provided.

The changes to the drug substance manufacturing process during development include change in the site of manufacture, scale-up, chromatographic resins and changes in the filters, elimination of animal derived raw materials and changes in the dosage form. Viral safety capacity was improved.

The approaches used to assess the comparability of Stelara after implementation of specific changes included a retrospective analysis of the structural integrity of the molecule, an evaluation of its biological functionality, and a comparison of the stability data and degradation profiles.

The applicant performed two separate comparability exercises in order to ensure that the changes made in the manufacturing process for the final bulk did not affect the structural and functional integrity of ustekinumab.

The manufacturing process has been validated through manufacturing scale validation batches and representative reduced-scale studies. All process validation and evaluation data demonstrate that the final bulk manufacturing process operates in a consistent and robust state of control and yields product that reliably meets predetermined criteria for quality. All analytical methods used for process validation and evaluation have been qualified. The process validation studies include validation of the cell culture process, anion and cation exchange chromatographic steps, virus removal filtration in filters, concentration and diafiltration of the pre-formulated bulk, resin re-use studies for chromatographic steps, cleaning processes for protein A, anion and cation resins, transport and control of impurities and excipients.

#### *Characterisation*

##### A) Elucidation of Structure and Other Characteristics

The drug substance has been comprehensively characterised, using state-of-the-art methods for physico chemical characteristics.

##### A1) Physicochemical characterisation.

The primary, secondary and tertiary structures of ustekinumab were analysed by various techniques.

The applicant generated a molecular model developed from a combination of crystal structures of the Fab and Fc using standard X-ray crystallographic methods.

The complete aminoacid sequence of ustekinumab was verified by a combination of aminoacid analysis using Edman N-terminal sequence analysis, PNGase F and carboxypeptidase B treatment, peptide mapping and mass spectrometry.

The secondary and tertiary structures were analysed by far and near UV circular dichroism spectroscopy respectively. Analytical ultracentrifugation did not reveal any detectable tendency for self-association for ustekinumab.

Characterisation of glycosylation indicated that ustekinumab is N-glycosylated at a single site in each heavy chain Asn299. The N-linked structures consist of biantennal, core-fucosylated species with galactose and sialic acid heterogeneity.

ustekinumab is a complex biomolecule that exists as a mixture of isoforms with variations in mass and charge. The microheterogeneity results primarily from the presence of multiple N-glycan structures at Asn299 and from partial removal of heavy chain C-terminal lysine. IEF and cIEF profiles revealed 5 isoforms after carboxypeptidase B treatment.

#### A2) Biological function

The methods used for assessing *in vitro* biological activity are based on the ability of ustekinumab to bind directly to human IL-12 neutralizing its biological activity. These include in-vitro potency assay, binding (EIA) assay and Fc binding competition evaluation.

#### B) Impurities

Protein based impurities are detected and monitored primarily by cSDS or SDS PAGE and DW-SE-HPLC or SE-HPLC. Impurities detected were identified when sufficient quantities of material allowed.

Host cell protein impurities present requires the use of immunological tests such as the HCP immunoassay.

#### C) Degradants

Characterization of degradants and degradation pathways were investigated by forced degradation studies performed under conditions tailored to accelerate specific types of degradation, a batch of ustekinumab formulated drug product incubated at 40°C in the final vial presentation and forced degradation and stressed stability studies.

#### Specifications

The drug substance release specifications, including tests for identity, impurities, potency, quantity and general attributes, are acceptable and well justified. Reference standards have been well described and qualified.

The applicant committed to review the specifications once additional commercial manufacturing batches have been undertaken.

- Stability

The design of the stability program, including the testing intervals and storage temperature conditions are in accordance with current ICH guidelines. The tests chosen are a subset of tests from the release specifications selected for stability indicating properties.

#### Medicinal Product

- Pharmaceutical Development

Formulation development studies were performed in order to determine the pH and buffer to minimize size related degradation products and deamidation and to achieve an optimal thermal stability profile.

Sucrose was chosen as stabilizer/tonicifier to facilitate subcutaneous administration after formulation. These excipients were used in early clinical studies and have been shown to be well tolerated.

Polysorbate 80 was considered important to protect the protein from unfolding and aggregate formation particularly due to physical agitation.

The impact of metal ion spiking studies was also investigated since they may become introduced during manufacture and could affect protein stability or aggregation. The data are adequately reported and did not show any effect.

Having established histidine, sucrose and PS80 as optimal buffer, tonicifier and surfactant respectively, experiments were designed to optimise their concentrations.

The composition of Stelara 90mg and 45mg final vial product (FVP) includes Sucrose, L-histidine, Polisorbate 80 and Water for injection.

- Adventitious Agents

The viral safety of Stelara with respect to adventitious agents is assured through the design and control of the manufacturing process. Potential viral agents include endogenous retrovirus and adventitious agents. Raw material controls minimize the risk of contamination by adventitious agents, and clearance studies provide assurance that any potential endogenous or adventitious agents will be eliminated.

Viral clearance is achieved through chemical viral inactivation and physical removal of virus using chromatographic and filtration processes. These steps include a dedicated viral inactivation step (solvent/detergent [S/D] inactivation) and a dedicated removal step (virus filtration), in addition to the viral clearance achieved through two orthogonal chromatographic unit operations.

Reduced scale models of the chromatography steps and the dedicated viral inactivation and removal steps were used to evaluate clearance of ERV, poliovirus Type 1 (poliovirus), pseudorabies virus (PRV), and reovirus-3 (reovirus). Initially, the S/D inactivation data for PRV was not considered sufficiently reassuring. By request, the applicant provided additional data on studies performed. The new results showed a low efficacy towards the inactivation of this virus. The applicant explains these low results by the impact of temperature used. Despite the results for the S/D step, it should be acknowledged that overall claimed PRV and ERV clearance across the Stelara manufacturing process is considered adequate.

With respect to the nanofiltration step only poliovirus clearance was determined. The claimed clearance was considered unexpected for this kind of virus since it should be more efficiently removed by virus filter as it is dedicated to the elimination of small non-enveloped viruses.

Based on the lack of validation data for ERV clearance using the nanofilter, it was considered that viral validations should have been performed with a larger panel of viruses including retroviruses and parvoviruses. With this respect, the Applicant provided during the procedure additional data on virus filter clearance of retroviruses using XuMLV as the test virus. The results provide some assurance that a similar clearance of ERV could be achieved with the virus filter under the same conditions. In addition, to further assure that the virus filter is robust, the Applicant will undertake a post-approval study using a parvovirus model virus MMV. Considering the validation data provided, it was concluded that the overall viral clearance of the manufacturing process for Stelara is sufficient.

The applicant provided virus clearance data for affinity chromatography and anion exchange resins at the end of the validated resin re-use. Interim results confirm that adequate virus clearance is maintained. The applicant commits to finalise the studies using two additional resin lots.

The routine manufacture of Stelara does not involve any human or ruminant animal-derived material. Therefore, no TSE safety issues arise from this.

- **Manufacture of the Product**

The drug product is manufactured by Cilag AG, Schaffhausen, Switzerland, operated in accordance to current EU good manufacturing practices (GMP).

The drug product manufacturing process consists of a sterilization filtration and aseptic filling into vials. The drug product is presented as a solution for injection containing 90 mg/ml ustekinumab, L-histidine, sucrose, polysorbate 80 and water for injection. The drug product is presented in two doses, a 45 mg vial (0.5 mL) and 90 mg vial (1.0 mL).

Critical process parameters were identified and documented as part of a risk assessment performed as outlined in ICH Q9.

Validation of the commercial process was performed on 3 batches.

The media fill and process validation results, lot-to-lot consistency data and critical process controls have shown that the sterile filtration and aseptic filling process are robust and well controlled and that the drug product can be consistently manufactured.

The manufacturing process is controlled by a series of critical process parameters (CPPs), in-process controls (IPCs), critical quality attributes (CQAs) and other product characteristics. These parameters were determined following clinical manufacturing experience by means of a risk assessment, and parameters categorized and parameters set.

- **Product Specification**

The final product release and shelf life specifications, including tests for identity, impurities, potency, quantity and general attributes were provided.

The applicant commits to review the final drug product specifications when data is available after 10 full scale commercial batches.

- **Stability of the Product**

Real time and accelerated stability studies were initiated in accordance with ICH guidelines to monitor the time-temperature stability of phase 3 and validation batches.

Based on the data provided, the approvable shelf-life for the drug product is 12 months at 2-8 C.

### **Discussion on chemical, pharmaceutical and biological aspects**

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

Cell line development is well described and documented. The resulting master and working cell banks have been extensively characterised, with respect to integration sites, copy number, sequencing and microbiological and viral safety. The cell bank was found to contain retrovirus-like particles by transmission electron microscopy (TEM), that have been shown to be defective, and for which the purification processes have been shown to be effective in removing. These retrovirus-like particles are expected in murine Sp2/0 cells.

Cell culture conditions and in-process controls are sufficiently described and are considered appropriate.

Overall the up-stream manufacturing and purification processes and controls in place for the drug substance are well described. The production processes of the drug substance and the capacity of the process to remove DNA, host cell protein, residual Protein A and cell culture additives have been suitability validated.

Extensive product characterisation has been undertaken including primary sequence analysis, oligosaccharide and sialic acid analysis, charge heterogeneity, size distribution and structural isoforms. The Stelara characterisation undertaken by the company was extensive, as was the work done on product and process related impurities.

The drug substance release specifications are acceptable and well justified and all methods adequately validated. Reference standards have been well described and qualified. Current stability data for Stelara drug product support the 12 months shelf life at 2-8°C.

The pharmaceutical development of the finished product and the manufacturing process of the finished product have been extensively described and is considered adequately controlled and validated. The drug product specifications have been justified.

The overall viral clearance of the manufacturing process for Stelara is sufficient based on the validation data provided on the S/D inactivation, nanofiltration and chromatographic steps.

It was noted that the applicant have not validated the nanofiltration step for the removal of ERV. The data provided on poliovirus model and the data provided on retrovirus XuMLV provide some assurance that a similar clearance of ERV could be achieved with the nanofilter under the same conditions. In addition, to further assure the nanofiltration step is robust the applicant will undertake a post-approval study using a parvovirus model virus MMV.

## 2.3 Non-clinical aspects

### Introduction

#### Pharmacology

- Primary pharmacodynamics

The pharmacology of ustekinumab was characterised using investigations of target binding interactions, mechanism of action, functional effects of neutralisation, species cross-reactivity and *in vivo* activity supporting a psoriasis indication.

ustekinumab is a fully human monoclonal antibody that is designed to neutralize the biological activities of the human interleukin cytokines IL-12 and IL-23. It was shown to have comparable binding and neutralising activity against human and cynomolgus macaque IL-12 and IL-23.

- Secondary pharmacodynamics

Secondary pharmacodynamic studies analysed *in vivo* activity of ustekinumab in animal models of immune-mediated diseases other than psoriasis.

CNTO 1275 (STELARA, ustekinumab) was pharmacologically active in non-human primates in a marmoset experimental autoimmune encephalomyelitis model (EAE) and was effective in suppressing EAE incidence and severity in marmosets. CNTO 1275 (STELARA, ustekinumab) delayed white matter demyelination and suppressed inflammation of pre-existing brain lesions in marmoset EAE.

IL-12 has been shown to antagonise immune responses mediated through Th2 T-cell lineages, which are thought to contribute to allergy and asthma immunopathologies. Thus, it was theoretically possible that neutralising IL-12 via CNTO 1275 (STELARA, ustekinumab) could exacerbate Th2-mediated diseases such as asthma. As a result two studies were conducted in an acute asthma model in cynomolgus monkeys, which revealed that CNTO 1275 (STELARA, ustekinumab) did not exacerbate

the asthmatic response or cellular responses after aerosol antigen challenge. Thus, CNTO 1275-related exacerbation of Th2-mediated disease was not observed.

- Safety pharmacology programme

No adverse effects of ustekinumab were observed in safety pharmacology evaluations following single and repeated dosing in cynomolgus monkeys via intravenous or subcutaneous routes of administration at doses up to 45 mg/kg. No adverse effects of ustekinumab were noted in cardiovascular evaluations of juvenile F1 monkeys exposed to ustekinumab indirectly following treatment of their respective dams. Cardiovascular/respiratory evaluations following single and repeated dosing with CNTO 1275 (STELARA, ustekinumab) at doses up to 45 mg/kg in monkeys showed no CNTO 1275-related findings.

There were no ECG findings in juvenile monkeys exposed to CNTO 1275 (STELARA, ustekinumab) indirectly following administration of CNTO 1275 (STELARA, ustekinumab) at doses up to 45 mg/kg during gestation and lactation.

No CNTO 1275-related effects on heart rate or capillary refill times were observed, nor in histopathology evaluations of cardiac tissue. Taken together, the data generated in toxicity studies did not suggest a relationship between CNTO 1275 (STELARA, ustekinumab) administration and changes in ECG intervals or identify cardiovascular safety issues. There were no findings in the CNS and no changes in body temperature. No CNTO 1275-related changes in behaviour were recorded.

Data from cardiovascular and respiratory endpoints in toxicity studies, post-mortem cardiac observations, *in vitro* binding data from pharmacology studies and from the human tissue cross-reactivity study confirmed that there were no cardiovascular safety signals in the toxicology program.

- Pharmacodynamic drug interactions

It was acknowledged that, because of the high binding specificity of CNTO 1275 (STELARA, ustekinumab) for its target, IL-12/23p40, it is unlikely to have pharmacodynamic interactions with co-administered drugs. Thus, no non-clinical pharmacodynamic drug interaction studies were conducted with CNTO 1275.

### **Pharmacokinetics**

The pharmacokinetics of ustekinumab were investigated mostly in the toxicity studies in cynomolgus monkeys following single and repeated subcutaneous administration at doses between 0.9 and 45 mg/kg. Studies to support modifications in the material and formulation during the development programme were also conducted. Traditional absorption, distribution, metabolism, and excretion (ADME) studies were not performed, which is consistent with ICH Topic S6 guidance for monoclonal antibodies (mAbs).

ustekinumab was absorbed into the systemic circulation with a mean  $T_{max}$  ranging from 2 to 7 days. Mean  $C_{max}$  and AUC values increased in an approximately dose-proportional manner. Mean  $t_{1/2}$  ranged from approximately 2 to 3 weeks. Following twice-weekly SC dosing, an estimated 5- to 10-fold accumulation in AUC and  $C_{max}$  was noted. Steady-state was reached by Week 13. The mean steady-state  $C_{max}$  value following a 45 mg/kg twice-weekly SC dose in monkeys (2347.08  $\mu\text{g/mL}$ ) was approximately 116-fold higher than the median  $C_{max}$  value following 4 weekly 90 mg SC doses in subjects with psoriasis (20.3  $\mu\text{g/mL}$ ). The absolute bioavailability was estimated to be 97% by cross-study comparison of a single-dose intravenous study and a single-dose subcutaneous study. The volume of distribution of ustekinumab in monkeys was 86 to 98 mL/kg following a single IV dose of 4.5 mg/kg, suggesting that the distribution of ustekinumab was mainly confined to the intravascular space, consistent with the volume of distribution for typical therapeutic IgG-based mAbs. ustekinumab was shown to cross the placenta into developing embryos. Fetal exposure to ustekinumab was proportional to the increase in SC dose administered to the dams.

Anti-ustekinumab antibodies were detected in single- but not in multiple-dose studies, which might have been related to the substantial presence of circulating ustekinumab during the observation period

or possible immune tolerance induction. Development of anti- ustekinumab antibodies was found to be associated with accelerated clearance and shortened half-life of ustekinumab in monkeys.

Acceptable pharmacokinetic and immunogenic comparability were shown between batches of material produced by two different cell lines and between liquid and lyophilised formulations.

### **Toxicology**

The safety studies include repeated-dose toxicity with periods of recovery in cynomolgus monkeys, and developmental and reproductive toxicity studies in cynomolgus monkeys and mice; a number of non-pivotal studies was also conducted. The choice of the cynomolgus monkey was justified on the basis of a tissue cross-reactivity study; there was also no evidence of binding to human tissues, indicating a low potential for off-target effects.

ustekinumab was generally well tolerated following IV doses up to 45 mg/kg/week for up to 1 month and following twice-weekly SC doses up to 45 mg/kg for 6 months. No target organ toxicity or delayed toxicity was found. In the last week of the 26-week chronic toxicity study, one animal developed bacterial enteritis and a possible contribution of ustekinumab to this infection could not be excluded. The mean steady-state C<sub>max</sub> value following a 45 mg/kg twice-weekly SC dose in monkeys was approximately 116-fold higher than the median C<sub>max</sub> value following 4 weekly 90 mg SC doses in subjects with psoriasis.

- **Single dose toxicity**

No single-dose toxicity studies were conducted. No evidence of acute toxicity was observed in single-dose PK studies.

- **Repeat dose toxicity (with toxicokinetics)**

Repeat-dose toxicity studies showed that CNTO 1275 (STELARA, ustekinumab) is generally well tolerated following IV doses up to 45 mg/kg/week for up to 1 month (Studies T-099-003 and T-099-004), and following twice-weekly SC doses up to 45 mg/kg for 6 months (Study T-2001-004). No CNTO 1275-related deaths or moribundity were observed. In the last week of the 26-week chronic toxicity study, one animal developed bacterial enteritis and a possible contribution of CNTO 1275 (STELARA, ustekinumab) to this infection could not be excluded. For all studies, there were no CNTO 1275-related physical signs, adverse effects on body weight, food consumption, body temperature or chemical pathology indices observed following CNTO 1275 (STELARA, ustekinumab) administration. There were no CNTO 1275-related findings in ophthalmoscopic and physical examinations.

Post-mortem examinations revealed no tumours or histopathological evidence of CNTO 1275-related pre-neoplastic changes in any organs or tissues.

- *26-week Subcutaneous Dose Toxicity and Toxicokinetic Study with CNTO 1275 (STELARA, ustekinumab) in Cynomolgus Monkeys with a 12-week Recovery Period (Study T-2001-004)*

CNTO 1275 (STELARA, ustekinumab) was dosed SC twice weekly to 3 dose groups of cynomolgus monkeys of 8/sex/group at doses of 22.5 or 45 mg/kg for 13 or 26 weeks. Control monkeys received SC injections of 0.9% sodium chloride for injection, in a dose volume of 0.5 mL/kg. The CNTO 1275 (STELARA, ustekinumab) treatment groups received SC injections of a 90 mg/mL solution of CNTO 1275 (STELARA, ustekinumab) in dose volumes of 0.25 and 0.5 mL/kg, in the 22.5 and 45 mg/kg groups, respectively.

Three animals/sex/group were sacrificed following 13 and 26 weeks of dosing and 2/animals/sex/group were sacrificed after a 12-week treatment free period following 26 weeks of dosing to evaluate reversibility, persistence, and/or delayed occurrence of any potential adverse effects. Safety pharmacology end-points were incorporated into the study design. Immunotoxicity measurements were incorporated into the study. Necropsy examinations were performed in weeks 14, 27 and 38.

No deaths or CNTO 1275-related physical signs of toxicity were observed and no effects on body weight or food consumption were noted.

One monkey in the 45 mg/kg group manifested physical signs associated with bacterial enteritis including low food consumption on Day 169 and non-formed faeces on Days 173 and 176. This monkey's body weight declined approximately 13% over 2-weeks going from 3.9 kg on Day 162 to 3.7 kg and 3.4 kg, respectively on Days 169 and 176. The Week 26 neutrophil count in this animal was increased 3.4-fold relative to its average untreated baseline value and was associated with an increase in percentage of neutrophils from approximately 43% to 85%, from average baseline to Week 26 values, respectively. Post-mortem findings confirmed the diagnosis of bacterial enteritis. In the ileum, bacteria were observed in the mucosa and moderate to severe acute inflammation with minimal congestion/haemorrhage were observed with minimal inflammation noted in the colon and rectum. The observation of bacteria within the mucosa is consistent with bacterial overgrowth and the diagnosis of bacterial enteritis was based on the observed inflammation of the small intestine and bacterial cultures. The collected mesenteric lymph node was observed to be large and microscopically, slight lymphoplasmacytic hyperplasia was noted. Consistent with bacterial infection and increased neutrophils, hyperplasia of the myeloid cells was noted in the bone marrow. Spontaneous repeated bouts of diarrhoea are often observed in control and stock cynomolgus monkeys. In this study, non-formed faeces were observed in all dose groups including controls.

In chemical pathology evaluations, small statistically significant differences between controls and CNTO 1275-treated groups were noted. These were considered incidental and of no toxicological significance because the magnitude of these changes was small; similar differences were noted in pre-dose values and/or there were no histopathological correlates.

Post-mortem, there were no CNTO 1275-related macroscopic or microscopic observations or organ weight changes.

There was no evidence of delayed toxicity in the animals sacrificed after 12 weeks of recovery.

- *A Multiple Intravenous Dose Toxicity Study with 12B75 in Cynomolgus Monkeys (Study no. T-099-004)*

CNTO 1275 (STELARA, ustekinumab) was administered by intravenous infusion to 3 dosage groups of 10 monkeys per group (5/sex/group) at dosages of 0 (0.9% saline), 9 or 45 mg/kg once weekly for 4 consecutive weeks. The IV infusions were administered in a dose volume of 5 mL/kg at a rate of approximately 3 mL/minute.

Safety pharmacology end-points were incorporated into the study design. In addition to standard measurements, lymphocyte subset (CD2, CD20, CD14, CD4 and CD8) were characterised in samples collected on Day 28 from all animals and on Days 58 and 59 from recovery females and males, respectively. Lymphoproliferative responses to concanavalin A (Con A) and phytohaemagglutinin A (PHA) were evaluated pre-dose, and on Days 28, 45 and 59/60. The animals were sacrificed one week after the fourth dose (3/sex/group) and after a 5-week post-dose recovery period (2/sex/group).

No deaths or CNTO 1275-related physical signs of toxicity were observed. Body weight, body temperature, food consumption and ophthalmic findings were not affected by CNTO 1275 (STELARA, ustekinumab) treatment. In females dosed at 45 mg/kg, slight but significant reductions in mean relative lymphocyte values and increases in mean relative neutrophil values were observed on Day 28 and corresponded to significant changes in absolute lymphocyte and neutrophil counts.

To understand better the toxicological significance of these observations, lymphocyte and neutrophil differential values in the female monkeys given 45 mg/kg on the Day 28 were compared with the pre-dose values. Only one female monkey (No. 3102) showed a marked decrease in the percentage of lymphocytes and increases in neutrophil percentages in the Day 28 differentials. The differentials were relatively unchanged from pre-dose values for the other females. No increases in immature cells of neutrophil lineage (band neutrophils, myelocytes or metamyelocytes) were observed in any animal of this group. No corresponding changes were observed in the male monkeys dosed at 45 mg/kg at any

time during the study. Lymphocyte and polymorphonuclear leukocyte (PMN) values in the 45 mg/kg females at Day 9 (2 days after the second dose) and in the 2 recovery animals on Day 58 were comparable to pre-dose values. No changes were noted in the 45 mg/kg females in lymphocyte subset analyses, lymphoproliferative responses to the T-cell mitogens, lymphoid organ weights or histopathology. The peripheral blood differential changes observed in female monkeys dosed at 45 mg/kg were considered likely to be related to stress-induced margination of the circulating leukocytes. Based on consideration of observations during a blinded peer review of lymphoid tissues; the absence of corresponding changes in male monkeys; absence of corresponding differences between control and high-dose females with respect to numbers of immature granulocytes, specific lymphocyte subsets, lymphoid organ weights, histopathology or lymphoproliferative responses, the observed changes in lymphocyte and neutrophil differential values are not considered of toxicological significance.

No CNTO 1275-related changes in organ weights were noted. There were no CNTO 1275-related macroscopic or microscopic findings at the end of dosing necropsy (1 week after administration of the fourth dose) or recovery necropsy (5 weeks after administration of the fourth dose).

It was noted from the report of the 6-month toxicity study that antibodies to CNTO 1275 (STELARA, ustekinumab) were detected in 15 out of 16 monkeys in the saline treatment group. Antibodies to CNTO 1275 (STELARA, ustekinumab) were initially of low titre, but increased until Week 30, after which titres declined. The immune responses were shown to bind specifically to CNTO 1275, and not to other similar immunoglobulin proteins. Toxicokinetic data (Centocor Technical Report CP2002T-091) did not reveal exposure to CNTO 1275 (STELARA, ustekinumab) in the saline treatment group; however there were no blood samples available for toxicokinetic analyses between Days 17 and 71. The applicant reported that review of the dosing procedures did not indicate any procedural deficiencies that could have resulted in accidental exposure to CNTO 1275. Therefore, there is no explanation for the immune antibody response results observed in the saline-treated monkeys.

As regards the 1-month study, the section of the peer review report covering the altered differential count is copied below:

‘The most dramatic change of neutrophil increase and lymphocyte decrease in the high dose female monkeys was noted in monkey No. 3102. The differential count did not reveal immature forms of neutrophils (metamyelocytes, myelocytes) consistent with a leukocytosis that was not related to increased hematopoiesis. These data could have been obtained from a stressed animal wherein margined leukocytes in vessels were released into the circulation. In order to support the peripheral blood differential cell count obtained with the clinical pathology data, a large vein in the pancreas (slide No. 12) was found that contained approximately 75 white blood cells mixed with erythrocytes that represented trapped blood (the pancreas was included on the slide containing the spleen and thymus). Other vessels containing blood were not available in the tissue sections for examination. Approximately 60% of the leukocytes were granulocytes and 40% were lymphocytes and monocytes rather than the 91% granulocytes and 7% lymphocytes observed in the data obtained from the peripheral blood. Application of the estimated numbers to the total leukocyte count would have eliminated the neutrophilia and lymphopenia reported for monkey No. 31 02.’

It was not clear whether this was unrelated to treatment or whether the animal in question was particularly sensitive to the effects of CNTO 1275 (STELARA, ustekinumab) and could be an indicator of an effect that might happen in more individuals were a larger population to be studied.

Toxicokinetic analysis of the 26-week SC repeat-dose study confirmed significant exposure of the monkeys to sustained high serum concentrations of CNTO 1275. Pharmacokinetic and immune response analyses indicated that CNTO 1275 (STELARA, ustekinumab) exposure was not limited by development of immune antibody responses to CNTO 1275.

The exposure levels following subcutaneous dosing are summarised in the applicant’s table copied from the pharmacokinetics tabular summary below:

2.6.5.4 PHARMACOKINETICS: ABSORPTION AFTER MULTIPLE DOSES

Test Article: 12B75/CNTO 1275

Location in CTD Study No. [PK Report No.] Species	4.2.2.2 T-2001-004 [CP2002T-091, CP2002T-091-A1, CP2002T-091-A2] <i>Macaca fascicularis</i>					
Vehicle/Formulation	CNTO 1275 Lot 5380-39: 90 mg/mL in 0.01 M sodium phosphate, 8.5% sucrose, 0.001% Tween 80, pH 6.0			CNTO 1275 Lot 5380-39: 90 mg/mL in 0.01 M sodium phosphate, 8.5% sucrose, 0.001% Tween 80, pH 6.0		
Route	Subcutaneous (2x/week x 26 weeks)			Subcutaneous (2x/week x 26 weeks)		
Gender (M/F)/Number of Animals	8M/8F			8M/8F		
Dose (mg/kg)	22.5			45		
Sample	Serum			Serum		
Analyte	CNTO 1275			CNTO 1275		
Assay	ELISA			ELISA		
Pharmacokinetic Parameters <sup>a</sup>	Day 1	Week 13	Week 26	Day 1	Week 13	Week 26
C <sub>max</sub> (µg/mL)	370.11 ± 197.51 2.00 (0.25-3.00)	1516.58 ± 617.25 0.25 (0.08-2.00)	1419.13 ± 493.65 1.50 (0.08-3.00)	672.64 ± 366.79 2.00 (0.25-3.00)	2238.59 ± 327.52 2.00 (0.08-2.00)	2347.08 ± 660.48 2.00 (0.25-3.00)
t <sub>max</sub> (day) <sup>b</sup>						
AUC <sub>0-t</sub> (µg × day/mL)	765.25 ± 436.75	4107.50 ± 798.28	3660.79 ± 1060.79	1424.23 ± 700.72	5975.10 ± 965.81	6185.90 ± 1500.47
AUC (µg × day/mL)	ND	ND	ND	ND	ND	ND
t <sub>1/2</sub> (day)	ND	ND	13.27 ± 4.30	ND	ND	11.60 ± 1.95
Ratio (C <sub>max</sub> ) <sup>c</sup>	ND	ND	5.98 ± 2.84	ND	ND	4.71 ± 2.53
Ratio (AUC) <sup>d</sup>	ND	ND	10.70 ± 8.78	ND	ND	5.70 ± 2.61
Additional Information	C <sub>max</sub> and AUC(0-t) appeared to increase with dose. Steady state concentrations were achieved by Week 13.					

<sup>a</sup>Mean ± SD, unless otherwise noted

<sup>b</sup>Median (range) values

<sup>c</sup>Ratio (C<sub>max</sub>) = [C<sub>max</sub> after last dose (Week 26)] / [C<sub>max</sub> after first dose (Day 1)]

<sup>d</sup>Ratio (AUC) = [AUC<sub>0-t</sub> value after the last dose (Week 26)] / [AUC<sub>0-t</sub> value after the first dose (Day 1)]

ND – Not Determined

No Serum CNTO 1275 (STELARA, ustekinumab) (< 0.19 µg/ml) was found in control samples.

Systemic exposure to CNTO 1275 (STELARA, ustekinumab) increased with dose; a 2-fold increase in dose resulted in an approximately 1.7-fold increase in C<sub>max</sub> and AUC. The mean trough concentrations on Day 166 for 25 and 50 mg/kg were 1335.58 and 1794.02 µg/ml respectively. Accumulation ratios for AUC (0-72h) were approximately 10.70 and 5.70 after twice weekly dosing of the 22.5 and 45 mg/kg CNTO 1275 (STELARA, ustekinumab) for 26 weeks, respectively. The mean value of peak to trough ratio at steady state was 1.43.

Toxicokinetic analysis of the 1-month IV repeat-dose study revealed that CNTO 1275 (STELARA, ustekinumab) accumulated in the sera with repeated weekly dosing at 9 or 45 mg/kg. The mean maximum serum concentrations observed in the 9 and 45 mg/kg groups were approximately 540 µg/mL and 3600 µg/mL, respectively in samples obtained 2 h following the last dose. Because of the high concentrations of CNTO 1275 (STELARA, ustekinumab) in serum samples, immune response analyses were not performed because high serum concentrations of CNTO 1275 (STELARA, ustekinumab) interfere with detection of monkey anti-CNTO 1275 (STELARA, ustekinumab) antibodies.

The maximum mean serum concentrations are presented in the applicant's table copied from the pharmacokinetics tabular summary below:

2.6.5.4 PHARMACOKINETICS: ABSORPTION AFTER MULTIPLE DOSES (CONTINUED)

Test Article: CNTO 12B75/CNTO 1275

Location in CTD Study No. [PK Report No.] Species Vehicle/Formulation	4.2.2.2 T-099-004 [REStr161.as REStr161.as-A1] <i>Macaca fascicularis</i>					
	12B75 Lot 052189, 9 mg/mL in 0.01 M sodium phosphate and 0.15 M sodium chloride, pH 6.0 Intravenous (qwk x 4 weeks)			12B75 Lot 052189, 9 mg/mL in 0.01 M sodium phosphate and 0.15 M sodium chloride, pH 6.0 Intravenous (qwk x 4 weeks)		
Route	5M/5F			5M/5F		
Gender (M/F)/Number of Animals	9			45		
Dose (mg/kg)	Serum			Serum		
Sample (whole blood, plasma, serum, etc.)	12B75 EIA			12B75 EIA		
Analyte	Following first dose			Following first dose		Following fourth dose
Assay	284.20 ± 72.5	417.3 ± 86.3	539.8 ± 94.8	1570 ± 553	3098 ± 497	3628 ± 1285
Pharmacokinetic Parameters	N/A			N/A		
$C_{max}$ (µg/mL)	N/A			N/A		
$t_{max}$ (day) median	N/A			N/A		
AUC <sub>0-last</sub> (µg × day/mL)	N/A			N/A		
AUC (µg × day/mL)	N/A			N/A		
$t_{1/2}$ (day)	15.9 ± 10.1			10.0 ± 2.3		
Clearance (mL/kg/day)	N/A			N/A		
Volume of Distribution (mL/kg)	N/A			N/A		
Bioavailability (%)	N/A			33.3 ± 13.5		
Additional Information	12B75 concentrations increased following each weekly IV dose. 12B75 concentrations increased with increased dose					

N/A – Not Applicable

*It was accepted that adequate exposure of the animals in the toxicity studies has been demonstrated.*

- Genotoxicity

Genotoxicity tests were not conducted.

- Carcinogenicity

In accordance with the guideline entitled ‘Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals’ (ICH S6), carcinogenicity studies were not performed. Direct evaluation of carcinogenic potential of CNTO 1275 (STELARA, ustekinumab) in carcinogenicity studies or rodent tumour immune surveillance models is precluded by the limited species reactivity of CNTO 1275 (STELARA, ustekinumab) which does not bind to or neutralise IL-12 or IL-23 from mice or rats. Thus, the potential for CNTO 1275 (STELARA, ustekinumab) to increase the risk of tumour development in humans cannot be evaluated directly in standard rodent carcinogenicity studies. Monitoring of malignancy will be a part of the comprehensive Risk Management Plan for CNTO 1275.

- Reproduction Toxicity

ustekinumab had no effects on male fertility as assessed by spermatogenic measurements only. The NOEL of ustekinumab for effects on male fertility was 45 mg/kg. There were no effects on mating behaviour or inhibin and testosterone serum concentrations, nor on sperm number, morphology, viability or motility.

Female fertility was investigated in a supportive study in mice using a rat-mouse chimaeric anti-mouse IL-12/23p40 monoclonal Antibody, CNTO 3913. The choice of this model was justified on the basis of the less robust reproductive characteristics of the monkey; it is accepted that the outcome is limited to the identification of potential female fertility hazards through blocking IL12/23 and not as a definitive estimate of risk for ustekinumab. There were no adverse effects of CNTO 3913 on female fertility indices and CNTO 3913 was well tolerated by female mice at doses up to 50 mg/kg.

In studies of embryo-fetal development in cynomolgus monkeys dosed intravenously or subcutaneously and pre-and post-natal development dosed subcutaneously, there were no effects on gestation, parturition, lactation or morphology or development of the offspring. The NOAEL was 45 mg/kg once weekly by the intravenous route and twice weekly by the subcutaneous route.

- Toxicokinetic data

Toxicokinetic analysis confirmed significant exposure of the monkeys to sustained high serum concentrations of ustekinumab. Pharmacokinetic and immune response analyses indicated that ustekinumab exposure was not limited by development of immune antibody responses to ustekinumab.

- Local tolerance

There was no evidence of local irritation by either the subcutaneous or intravenous routes.

- Other toxicity studies

Immunotoxicity evaluations revealed no adverse effects of ustekinumab on functional immune responses, circulating lymphocyte subpopulations or distribution of T- and B-lymphocytes in lymphoid tissue.

There are no toxicological issues arising from the impurities.

#### **Ecotoxicity/environmental risk assessment**

ustekinumab is not considered to pose any adverse environmental effects. Since the product is a protein, it is exempted from an Environmental Risk Assessment (ERA) under EMEA/CHMP/SWP/4447/00.

#### **Discussion on the non-clinical aspects**

The Applicant conducted an acceptable programme of toxicity studies. Only two dose levels of ustekinumab were studied and mostly only one species for the toxicology, but this was considered acceptable for this type of product. The duration of the repeat-dose studies was considered adequate to support a marketing authorisation.

ustekinumab was generally well tolerated under a regimen of twice weekly subcutaneous dosing at 45 mg/kg for 6 months in cynomolgus monkeys and adequate margins of exposure over the human clinical exposure were demonstrated. No target organs were identified and there was no delayed toxicity after dosing had stopped. The possibility of immune suppression could not be ruled out in the case of one animal in the 6-month study that developed bacterial enteritis.

It is noted that, in the 6-month repeat-dose study and the embryo-fetal developmental toxicity study, antibodies to ustekinumab were found in control samples. There is no clear explanation for this finding but it was accepted that it is possible to draw valid conclusions from these studies. It was also accepted that it is indeed unlikely that an explanation can be provided for this finding.

A general finding in the toxicity studies was that it was not possible to discern whether there had been an anti-antibody response to ustekinumab, although some animals were noted to have greater clearance than others. This was not considered to have invalidated the studies and the pharmacokinetic indices were considered to show that adequate exposure was demonstrated.

ustekinumab had no effects on male fertility as assessed by spermatogenic measurements only. In females there were no effects on gestation, parturition, lactation or morphology and development of the offspring.

## **2.4 Clinical aspects**

### **Introduction**

The clinical development program of STELARA (ustekinumab) for the treatment of moderate to severe plaque psoriasis consisted of 5 studies with different formulations examining IV administration at a single dose and SC administration at single and multiple doses (both fixed and weight adjusted). The 2 pivotal Phase 3 studies C0743T08 [PHOENIX 1] and C0743T09 [PHOENIX 2] in which 1965 subjects were exposed to ustekinumab, included the formulation and dosing regimens intended for the commercial product. An overview of the studies used to derive population PK data is given below.

Table 1 Listing of CNTO 1275 clinical studies summarized in Module 2.7.2						
Study population	Study number	Study phase	Dose group(s)	Route of administration <sup>b</sup>	Number of subjects evaluated for PK <sup>d</sup>	Sampling scheme <sup>a</sup>
Psoriasis	C0379T01	1	0.09 mg/kg single dose	IV	4	Intensive
			0.27 mg/kg single dose	IV	4	
			0.9 mg/kg single dose	IV	5	
			4.5 mg/kg single dose	IV	5	
	C0379T02	1	0.27 mg/kg single dose	SC	5	Intensive
			0.675 mg/kg single dose	SC	4	
			1.35 mg/kg single dose	SC	4	
			2.7 mg/kg single dose	SC	4	
	C0379T04	2	45 mg single dose	SC	23	Intensive
			90 mg single dose	SC	27	
			45 mg multiple dose	SC	23	
			90 mg multiple dose	SC	21	
C0743T08 (PHOENIX 1)	3	45 mg multiple dose	SC	378 <sup>c</sup>	Sparse	
		90 mg multiple dose	SC	375 <sup>c</sup>		
C0743T09 (PHOENIX 2)	3	45 mg multiple dose	SC	606 <sup>c</sup>	Sparse	
		90 mg multiple dose	SC	606 <sup>c</sup>		
Multiple sclerosis	C0379T03	1	0.27 mg/kg single dose	SC	4	Intensive
			0.675 mg/kg single dose	SC	4	
			1.35 mg/kg single dose	SC	4	
			2.7 mg/kg single dose	SC	4	
	C0743T06	2	27 mg multiple dose	SC	30	Sparse
			90 mg multiple dose	SC	61	
			180 mg multiple dose	SC	30	
Crohn's disease	C0379T07	2	4.5 mg/kg single dose	IV	59	Intensive
			90 mg multiple dose	SC	61	
Healthy Subjects	C0743T11	1	90 mg single dose	SC	31	Intensive
<sup>a</sup> Intensive sampling schemes enable determination of the full PK profile using a non-model-based approach (eg, non-compartmental analysis). Sparse sampling schemes require a model-based approach to characterize the full PK profile. <sup>b</sup> SC = subcutaneous, IV = intravenous <sup>c</sup> Subjects randomized to placebo who crossed-over to CNTO 1275 were included. <sup>d</sup> For C0379T07, C0743T08 and C0743T09, this includes all subjects who received at least 1 administration of CNTO 1275. For C0379T06 the highest sample numbers throughout the sampling timepoints was used.						

## GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

## Pharmacokinetics

Validated methods of enzyme-linked immunosorbant assay (ELISA) and electrochemiluminescent immunoassay (ECLIA) were used to determine the serum CNTO 1275 (STELARA, ustekinumab) concentrations in the clinical studies. An enzyme immunoassay (EIA) method was developed and validated to detect antibodies to ustekinumab in human serum samples. Human serum samples from clinical studies identified as containing antibodies to ustekinumab were further characterized for the ability of those antibodies to neutralize the bioactivity of ustekinumab using a cell-based assay.

- Absorption/ Bioavailability

From the phase 1 trial C0379T02, which used SC dosing, based on the dose-normalized AUC from the IV study C0379T01, the bioavailability (F) of ustekinumab was estimated to be 57.2% (range: 24.3% to 95.0%) following a single SC administration (0.27 mg/kg to 2.7 mg/kg).

- Distribution

The final population PK model was developed using the combined data from both phase 3 trials. The final model was found to be robust after validation by bootstrap method and visual predictive check approach. In the final model with combined data set, the population CL/F and V/F values were estimated to be 0.465 L/d and 15.7 L, respectively. The median half-life of ustekinumab was estimated to be 21.6 days. There was no evidence of accumulation of ustekinumab within the dose ranges and frequency used in the phase 3 trials. The modelling used to derive population PK data correlated with the results from individual studies.

On population PK modelling the factors found to be statistically significant ( $p < 0.005$ ) in increasing the CL/F of ustekinumab were increased weight ( $>100\text{kg}$ ), diabetes and positive immune response to ustekinumab.

- Elimination

The median CL values following a single intravenous injection ranged from 1.8 mL/day/kg to 2.3 mL/day/kg in subjects with psoriasis (C0379T01). The median CL/F following a single SC administration was 3.0 mL/day/kg given an absolute bioavailability (F) of 57.2%, this is consistent with the CL value reported in the IV study C0379T01. The CL/F values were somewhat higher in subjects with psoriasis.

- Dose proportionality and time dependencies

The mean serum concentrations of ustekinumab generally peaked at weeks 1 to 2 following a single SC administration and then declined exponentially through weeks 12 to 24. For subjects who received 4 weekly SC administrations, the median  $t_{1/2}$  was approximately 21 days to 29 days, which is comparable to the  $t_{1/2}$  after a single SC administration in the same study (approximately 20 days to 21 days). These results demonstrated that the  $t_{1/2}$  remains constant after multiple dose regimens. In the 2 Phase 3 studies in subjects with psoriasis (PHOENIX 1 and PHOENIX 2), serum concentrations were comparable through Week 28 at each of the 2 dose levels (45 mg and 90 mg). Overall, there was no evidence of accumulation at the doses used.

- Special populations

*Weight:* Pharmacokinetic modelling in psoriasis subjects above and below 100kg revealed lower serum levels and AUC of ustekinumab (about 30% lower) in subjects  $>100\text{kg}$ . This difference between subjects based on weight also correlates with lower clinical efficacy.

The PK model also predicted mean CL/F and V/F values of ustekinumab increased with the increase of body weight. (CL/F and V/F values were 0.44 L/d and 14.2 L, respectively, in subjects  $\leq 100\text{ kg}$ , and were 0.68 L/d and 19.5 L, respectively, in subjects  $> 100\text{ kg}$ ).

*Elderly:* The majority of subjects in the population PK analysis were non-elderly subjects ( $<65\text{ yrs}$  of age): 106 elderly (5.5%) subjects versus a total of 1831 non-elderly (94.5%) were included in the analysis and therefore it was difficult to exclude an age effect. However the posology and administration are the same (see section 4.2 of the SPC).

*Children:* ustekinumab was not tested in subjects under 18years of age. As a result, Stelara is not recommended for use in children below age 18 (Section 4.2 of the SPC).

Other factors were evaluated for their possible effect on CL/F and/or V/F of ustekinumab:

- *Impaired renal function:* As creatinine clearance increased with weight and was higher in males, the relevance of the combined data was uncertain and the absolute effect was small;

- *Impaired liver function:* As the differences noted are small, the relevance was uncertain;

- *Gender:* A small difference was detected, which was considered unlikely to be significant;

- *Race:* 1793 (92.6%) Caucasian subjects and 144 (7.4%) non-Caucasian subjects were included in the population PK analysis. Race did not have a significant effect on the model-predicted CL/F estimate of ustekinumab. Although the non-Caucasians subjects had an 11.1% lower V/F estimate than Caucasians this was not considered to be clinically meaningful.

- Pharmacokinetic interaction studies

A total of the 28 most frequently used concomitant medications were evaluated for potential drug-drug interactions. None of the concomitant medications had a significant effect on the CL/F of ustekinumab.

## Pharmacodynamics

- Mechanism of action

IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 and IL-23 participate in immune function by contributing to NK cell activation and CD4+ T cell differentiation and activation. However, abnormal regulation of IL-12 and IL-23 has been associated with immune-mediated diseases, such as psoriasis. ustekinumab is a fully human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23 and shows no cross-reactivity to structurally related proteins IL-6, IL-6sR, CNTFR (Ciliary neurotrophic factor), and IL-11R. ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing these cytokines from binding to their IL-12Rβ1 receptor protein expressed on the surface of Natural killer (NK) and CD4+ T cells. ustekinumab cannot bind to IL-12 or IL-23 that is pre-bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement or antibody mediated cytotoxicity of the receptor-bearing cell. ustekinumab prevents IL-12 and IL-23 contributions to immune cell activation, such as intracellular signaling and cytokine secretion and is therefore believed to interrupt signaling and cytokine cascades that are central to psoriasis pathology.

- Primary pharmacology

Study DIS.RES.DRR.005 was conducted to identify the IL-12 subunit specificity, epitope affinity, and stoichiometry of ustekinumab binding using ELISA and nitrocellulose membrane binding analysis. ustekinumab was found to be specific for the p40 subunit of IL-12 and did not bind to the structurally related proteins IL-6, IL-6sR, CNTFR, and IL-11R. Crystal structure and mutational analysis elucidated the molecular binding interactions as discontinuous residues located in the D1 domain of IL-12/23p40. BIAcore analysis showed that ustekinumab binds human IL-12 and IL-23 with the expected mAb/ligand 2:1 stoichiometry and with high affinity to IL-12 and IL-23.

Study DIS.RES.DRR.006 examined the relationship between ustekinumab binding and natural ligand binding to the IL-12 and IL-23 receptors. ustekinumab was shown to prevent IL-12 or IL-23 binding to the IL-12Rβ1 receptor chain of IL-12 and IL-23 receptor complexes. ustekinumab inhibited binding of IL-12 or IL-23 to IL-12Rβ1 expressed on the cell surface either alone or in functional IL-12Rβ1/β2 and IL-12Rβ1/23R dual receptor complexes. ustekinumab did not bind to IL-12 or IL-23 that is pre-bound to cell surface receptors or stimulate complement dependent cytotoxicity responses. Other than these studies and the demonstration of their clinical consequences in terms of benefit in plaque psoriasis there was no exploration of the primary pharmacology of ustekinumab. Although the mechanism of action is known, the PD measurements did not show any significant difference after treatment.

- Secondary pharmacology

As with the primary pharmacology there was sparse exploration on the secondary pharmacology. There was limited evidence that ustekinumab does not bind to receptors other than IL-12 and IL-23, or that there is take-up by human tissues *ex-vivo*.

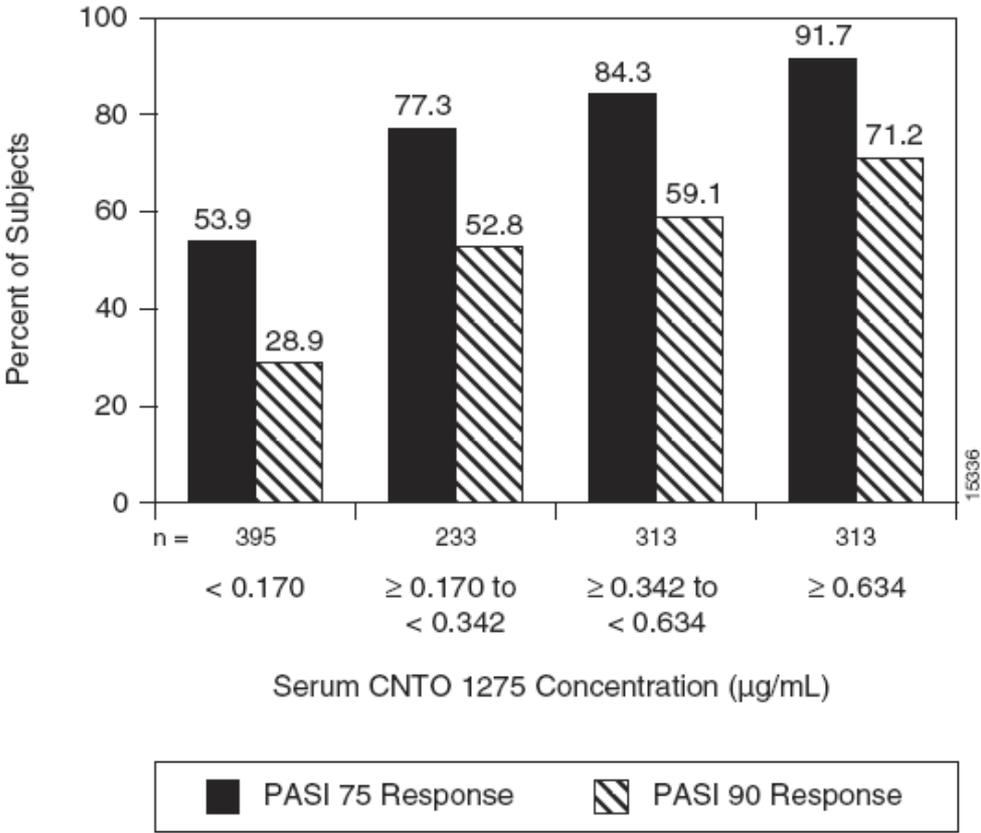
- Relationship between plasma concentration and effect

Although multiple cytokines were measured to detect PD effects, there were no marked differences noted post-treatment. This suggests that either the timing was too early or that ustekinumab exerts its effects without impairing the systemic immune system sufficiently to be detected with these assays. Further studies on the effect of Stelara on vaccination responses will be conducted as Follow-Up Measure.

Although the PD data (IL-12 related gene, serum cytokines IFNγ, IL-2, TNFα and lymphocyte surface markers) did not show any major changes when tested, the clinical response did show a correlation with increasing dose. The PASI index was used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score from 0 to 72, where higher

scores represent more severe disease, and is calculated taking into account the area of the body involved, and the degree of erythema, induration and scaling of each lesion. Subjects who achieved  $\geq 75\%$  improvement from baseline are PASI 75 responders, those who achieved a 90% improvement are PASI 90 responders. When the PASI responses of subjects were plotted against their trough serum ustekinumab concentrations, a positive correlation was demonstrated.

**Figure 1 Percent of subjects achieving PASI 75 and PASI 90 responses at Week 28 by trough serum ustekinumab concentrations at Week 28 in psoriasis Phase 3; treated subjects randomized to ustekinumab at Week 0**



There was evidence that ustekinumab level correlates with the clinical response and that there is no accumulation with the dose range tested. In addition, the PK data demonstrated that patients over 100kg have lower serum trough levels compared with those under 100kg. The modelling used to derive population PK data correlated with the results from individual studies.

**Clinical efficacy**

The application consists of two placebo-controlled pivotal trials (PHOENIX 1 and PHOENIX 2) as well as a supportive earlier phase trial (please see table below).

<b>Table 1 Psoriasis clinical studies</b>		
Study Total follow-up (Follow-up during placebo-control period)	Severity of Plaque Psoriasis	Treatment Group (# of subjects)
<b>PHASE 1</b>		
C0379T01 <sup>a</sup> 16 weeks (none)	BSA involvement ≥ 3%	Weight adjusted doses: - 0.09 mg/kg single IV dose (n = 4) - 0.27 mg/kg single IV dose (n = 4) - 0.9 mg/kg single IV dose (n = 5) - 4.5 mg/kg single IV dose (n = 5)
C0379T02 <sup>a</sup> 24 weeks (24 weeks)	BSA involvement ≥ 3%	Weight adjusted doses: - Placebo (n = 4) - 0.27 mg/kg single SC dose (n = 5) - 0.675 mg/kg single SC dose (n = 4) - 1.35 mg/kg single SC dose (n = 4) - 2.7 mg/kg single SC dose (n = 4)
<b>PHASE 2</b>		
C0379T04 <sup>a</sup> 52 weeks (20 weeks)	PASI ≥ 12; BSA involvement ≥ 10%	Fixed doses: - Placebo (n = 64) <sup>b</sup> - Placebo → 90 mg single SC dose (n = 47) - 45 mg single SC dose (n = 64) - 90 mg single SC dose (n = 64) - 45 mg weekly x 4 SC doses (n = 64) - 90 mg weekly x 4 SC doses (n = 64)
<b>PHASE 3</b>		
C0743T08 <sup>a</sup> (PHOENIX 1) ≥ 52 weeks <sup>c</sup> (12 weeks)	PASI ≥ 12; BSA involvement ≥ 10%	Fixed doses: - Placebo (n = 255) - Placebo → 45 mg regimen <sup>d</sup> (n = 123) - Placebo → 90 mg regimen <sup>d</sup> (n = 120) - 45 mg SC Weeks 0, 4 then q12w (n = 255) - 90 mg SC Weeks 0, 4 then q12w (n = 256)
C0743T09 <sup>a</sup> (PHOENIX 2) 28 weeks (12 weeks)	PASI ≥ 12; BSA involvement ≥ 10%	Fixed doses: - Placebo (n = 410) - Placebo → 45 mg regimen <sup>d</sup> (n = 197) - Placebo → 90 mg regimen <sup>d</sup> (n = 195) - 45 mg SC Weeks 0, 4 then q12w (n = 409) - 90 mg SC Weeks 0, 4 then q12w (n = 411)
BSA = body surface area; IV = intravenous; SC = subcutaneous; PASI = Psoriasis Area and Severity Index; q12w = every 12 weeks.		
<sup>a</sup> Additional details of study design, placebo crossover, and dose modifications are provided in <a href="#">Appendix A.1</a>		
<sup>b</sup> At Week 20, subjects in the placebo group received a single dose of 90 mg.		
<sup>c</sup> Includes all data available through the date the last subject completed the Week 52 visit (ie, through the end of the reporting period).		
<sup>d</sup> The placebo groups crossed over to receive 45 mg or 90 mg at Weeks 12 and 16 then q12w.		

The recruitment of subjects was not limited to those indicated in the SPC (i.e. adult patients with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA). However the randomisation of patients in both phase 3 trials included randomisation on the basis of weight and on the basis of whether there were < 3 or ≥ 3 conventional therapies to which the subject had an inadequate response, intolerance, or contraindication. This group constituted 11% and 16% of the total population in PHOENIX 1 and 2 respectively.

The efficacy of ustekinumab in the treatment of plaque psoriasis in adult patients is supported by analyses from 5 studies. Table 1 details the posology for each trial.

### ***Dose-response studies***

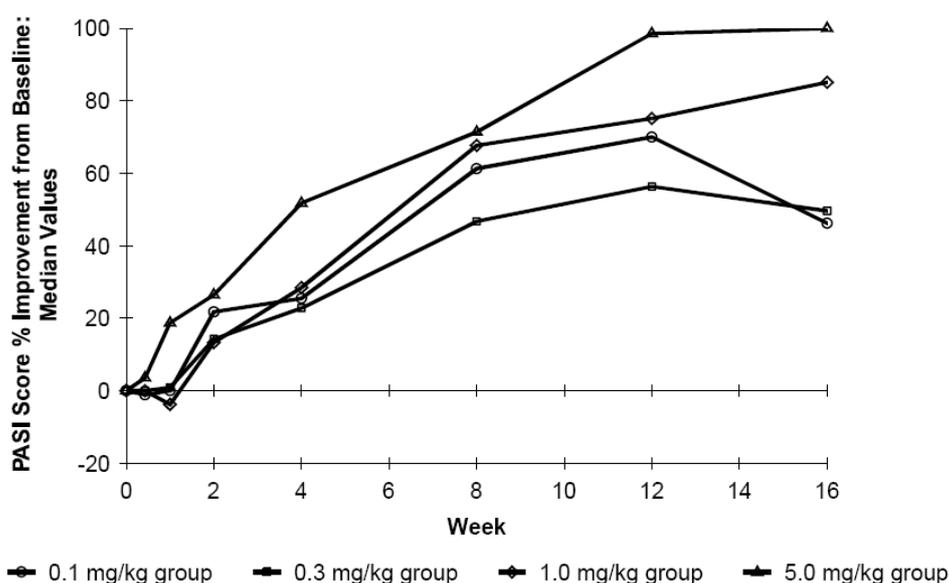
The range of doses of ustekinumab chosen for the first in human Phase 1 study in subjects with psoriasis was predicted to span subtherapeutic and therapeutic serum concentrations based on

preclinical data from nonhuman primate studies and in vitro neutralization analyses, and was supported by IV toxicology studies in primates that demonstrated no observed adverse effect level at doses 500-fold higher than the first dose tier studied in humans and 10-fold higher than the highest dose studied.

The results for [trial C0379T01](#) (single IV dose) are shown below (Figure 2).

Clinical efficacy of ustekinumab was evaluated by performing the Psoriasis Area and Severity Index (PASI), Physician's Global Assessment (PGA), and PSS (Psoriasis Severity Scale) measurements at multiple time-points. Examination of the PASI scores showed a clear tendency towards a dose-response, with no evidence of a response plateau over the tested dose range. Treatment responses as demonstrated by PASI score were generally first evident by 2 to 4 weeks after dosing. In general, maximum response to treatment was generally observed by week 12 and largely maintained at week 16. Because worsening of PASI scores at the end of follow-up was generally not evident, the duration of a single-dose IV treatment effect cannot be clearly estimated from this study.

**Figure 2:** Median percent improvements in overall PASI scores over time by treatment group.



Overall, a single IV infusion of ustekinumab produced clinically significant improvement in PASI and PGA, (physician global assessment grades lesions with regard to induration, scaling and erythema). The PGA is defined as (0) = cleared, (1) = minimal, (2) = mild, (3) = moderate, (4) = marked and (5) = severe) in subjects with moderate to severe psoriasis, and this improvement was generally sustained over the 16-week study period.

There was evidence for efficacy of ustekinumab from PASI and PGA scores compared with placebo. In addition there was evidence of efficacy in the DLQI score, a dermatology-specific QOL instrument designed to assess the impact of the disease on a subject's QOL, compared with placebo. It is a 10-item questionnaire that is used to assess 6 different aspects that may affect QOL: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The DLQI score is calculated by summing the score of each question, with an overall score ranging from 0 to 30; a lower DLQI score represents better QOL). The effect is delayed taking >6 weeks to achieve maximal effect, is weight and dose dependent, long-lasting (up to 12 weeks) and re-treatment is effective in those who did not respond initially.

PGA scores also showed a clinically meaningful improvement in the majority of subjects by weeks 8 to 12, with better therapeutic response observed in the 2 highest dose groups (0.9 and 4.5 mg/kg), suggesting a correlation of clinical response with dose of ustekinumab.

Results from [trial C0379T02](#) revealed improvement in PASI and PGA in subjects with moderate to severe psoriasis after a single SC administration of ustekinumab. The maximum effect of treatment

was observed between weeks 8 and 16 in all treatment groups. Clinically significant improvement was sustained in the 3.0 mg/kg treatment group throughout the 24-week study. Furthermore, the efficacy data generally suggested a positive correlation of extent and duration of clinical response with dose of ustekinumab.

The primary endpoint of [study C0379T04](#) was the proportion of PASI 75 responders at Week 12. More subjects in the ustekinumab groups had PGA scores of clear or excellent than subjects in the placebo group through Week 20. After placebo crossover, a majority (52.7%) of subjects in the placebo → 90 mg group scored clear or excellent on the PGA at Week 32.

At Week 12, subjects in each of the 4 ustekinumab groups had statistically significant and clinically meaningful improvements (decreases) in DLQI Dermatology Life Quality Index scores ( $p < 0.001$  for each CNTO 1275 (STELARA, ustekinumab) group compared with placebo).

### ***Main clinical studies***

The two Phase 3 studies (PHOENIX 1 [C0743T08] and PHOENIX 2 [C0743T09]) were designed to evaluate how the product should be used in the long-term management of psoriasis. These studies evaluated dosing regimens proposed for marketing and therefore provide the most relevant information.

## **METHODS**

### ***Study Participants***

**Study PHOENIX 1:** This was a multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of ustekinumab in the treatment of subjects with moderate to severe plaque psoriasis, and evaluating whether subjects who inadequately respond to an initial dosing regimen at q12w intervals would respond to more frequent drug administration at q8w intervals.

***Inclusion Criteria:*** Men and women 18 years of age or older were eligible to participate if they had a diagnosis of plaque-type psoriasis for 6 or more months, covering  $\geq 10\%$  of total body surface area (BSA), screening and baseline PASI score  $\geq 12$ , and were considered by the investigator to be candidates for phototherapy or systemic therapy. Subjects were to have had no history of active or latent TB on TB screening.

***Exclusion Criteria:*** The study excluded subjects with non-plaque psoriasis or drug-induced psoriasis. Previous users of ustekinumab or subjects who had had a serious reaction to mAbs were excluded from participation. Subjects who were pregnant, nursing, or planning pregnancy (both men and women) while enrolled in the study were to be excluded. The study excluded subjects with current signs or symptoms of severe, progressive, or uncontrolled medical conditions. Have ever received natalizumab or other agents that target alpha-4-integrin. Have received within 3 months prior to the first injection a live virus or bacterial vaccination. Subjects must agree not to receive a live virus or bacterial (including BCG) vaccination during the study or up to 12 months after the last study agent injection. Those with a history of severe anaphylaxis, asthma, severe infection, malignancy or transplantation were excluded.

To examine whether longer-term treatment with CNTO 1275 (STELARA, ustekinumab) would result in durable remissions, the duration of response and the need for maintenance therapy were evaluated using a randomized withdrawal design in which long-term PASI 75 responders (ie, achieved a PASI 75 response at Weeks 28 and 40) were randomized at Week 40 to maintenance therapy (q12w CNTO 1275) or withdrawal of therapy (placebo).

The study planned to randomize approximately 750 subjects at 60 sites. A total of 766 subjects were randomly assigned to treatment at 48 sites at Week 0.

This study is currently ongoing with a 5-year long-term extension phase.

**Study PHOENIX 2:** This was a multicenter, randomized, double-blind, placebo-controlled trial evaluating efficacy and safety of ustekinumab in the treatment of subjects with moderate to severe plaque psoriasis. The study planned to randomize approximately 1200 subjects at 75 sites. A total of 1230 subjects were randomly assigned to treatment at 70 sites at Week 0. The study is currently ongoing with a 5-year long-term extension phase.

Both studies were designed to evaluate the safety and efficacy of 2 dosing regimens of CNTO 1275:

- 45 mg at Week 0 and 4 followed by 45 mg q12w maintenance therapy (45 mg q12w regimen);
- 90 mg at Week 0 and 4 followed by 90 mg q12w maintenance therapy (90 mg q12w regimen).

Study PHOENIX 1: The safety and efficacy of these 2 regimens are to be evaluated during 4 study periods occurring over approximately 5 years:

- A 12-week placebo-controlled period;
- A subsequent 28-week *placebo crossover and active treatment period*;
- A randomized-withdrawal period begins at Week 40;
- A *long-term extension period* begins at Week 52 for an additional 4 years.

This report provided by the MAA primarily includes analyses from the first 3 of these 4 study periods, and includes all data available through the date the last subject completed the Week 52 visit (i.e. through the end of the reporting period).

Study PHOENIX 2: The safety and efficacy of these 2 regimens will be evaluated during 4 study periods occurring over approximately 5 years:

- A 12-week *placebo-controlled period*;
- A subsequent 16-week *placebo crossover and active treatment period*;
- A 24-week *dose schedule optimization period* beginning at Week 28;
- A *long-term extension period* begins at Week 52 for a total of approximately 4 years.

This report includes analyses from the first 2 of these 4 study periods, and includes all data available through Week 28, up to but not including, the Week 28 administration of study agent.

#### *Treatments*

Study PHOENIX 1: Patients were randomised to placebo, or 45 mg (Group 1) or 90 mg ustekinumab s.c. (Group 2) at Weeks 0, 4, and 16. At Week 12, subjects randomised to placebo were randomised to 45 mg or 90 mg ustekinumab at Weeks 12 and 16.

Randomisation was stratified by investigational site, weight ( $\leq 90$  kg or  $> 90$  kg), and whether there were less than 3 or at least 3 previous conventional therapies (i.e. psoralen plus UVA light, methotrexate, acitretin, cyclosporine) to which the subject had an inadequate response, intolerance, or contraindication.

At Week 40, patients in Groups 1 and 2 who were PASI 75 responders at Weeks 28 and 40 were randomised to continue maintenance therapy every twelve weeks or to placebo. The second randomisation was stratified by investigational site and baseline weight ( $\leq 90$  kg or  $> 90$  kg).

Study PHOENIX 2: Patients were randomised to placebo or to 45 mg (Group 1) or 90 mg ustekinumab s.c. (Group 2) at Weeks 0, 4, and 16. At Week 12, patients randomised to placebo were to receive 45 mg or 90 mg ustekinumab at Weeks 12 and 16. Pharmacokinetic, efficacy and safety variables were evaluated over twenty-eight weeks, and anti - ustekinumab antibody formation over twenty-four weeks.

#### *Objectives*

The primary objective of study PHOENIX 1 and study PHOENIX 2 was to evaluate the efficacy and safety of ustekinumab in the treatment of subjects with moderate to severe plaque psoriasis.

The secondary objectives of study PHOENIX 1 were to evaluate the maintenance of response with ustekinumab and to evaluate the impact of ustekinumab on QOL.

Secondary objectives of study PHOENIX 2 were to evaluate the impact of ustekinumab on quality of life and to evaluate dosing interval adjustment in subjects who inadequately respond to the starting dose regimen of ustekinumab. Results of this period of the study (Week 28 to Week 52) have been reported in the 52-Week CSR provided during the procedure.

#### *Outcomes/endpoints*

The primary endpoint of both study PHOENIX 1 and study PHOENIX 2 was the proportion of subjects who achieved improvement from baseline in PASI (Psoriasis Area and Severity Index) 75 response at Week 12.

Major Secondary Endpoints for both studies were: 1) The proportion of subjects with PGA (Physician's Global Assessment) score of cleared or minimal at week 12; 2) The change in DLQI

(Dermatology Life Quality Index) score from baseline at week 12; 3) Assessment at week 12 of PASI 50, PASI 90, PASI 100.

To evaluate the optimal treatment regimen with CNTO 1275, the Phase 3 program assessed:

- Initial efficacy of 2 different doses of CNTO 1275 (STELARA, ustekinumab) versus placebo through Week 12;
- Efficacy of 2 different doses of CNTO 1275 (STELARA, ustekinumab) administered as initial and maintenance therapy over time (through Week 40 in PHOENIX 1 and through Week 28 in PHOENIX 2);
- Efficacy of maintenance therapy (ie, maintenance therapy versus placebo after randomized withdrawal at Week 40) in PHOENIX 1.

In both Phase 3 studies, the placebo group crossed over to CNTO 1275 (STELARA, ustekinumab) at Week 12, so comparisons of initial CNTO 1275 (STELARA, ustekinumab) efficacy versus placebo are limited to 12 weeks.

Study PHOENIX 1: To evaluate longer term efficacy, psoriasis improvement was assessed over time by PASI and PGA from Week 12 through Week 40, after the placebo group crossed over to CNTO 1275. The efficacy of maintenance therapy was evaluated using a randomized withdrawal design. Multiple analyses were used to measure the efficacy of maintenance therapy, including the major secondary endpoint of time to loss of PASI 75 response. To evaluate the efficacy of retreatment, subjects withdrawn from therapy reinitiated their original CNTO 1275 (STELARA, ustekinumab) regimen when they experienced loss of therapeutic effect (ie, loss of 50% of their Week 40 PASI improvement) were assessed by PASI 75 response relative to week 0. To examine whether subjects who inadequately respond to q12w dosing may respond to dosing interval adjustment, subjects who were partial responders at Week 28 ( $\geq 50\%$  to  $< 75\%$  improvement in PASI from baseline) underwent dosing interval adjustment to q8w dosing and were assessed. Safety and efficacy analyses for subjects who adjusted to q8w administrations were observational in nature since no control group was available for comparison.

Study PHOENIX 2: To evaluate the maintenance of response, psoriasis improvement was assessed over time by PASI and PGA from Week 12 through Week 28. The impact of weight on psoriasis improvement PASI 75 response rates at Week 12 and through week 28 were analyzed by approximate body weight quartiles and subpopulations based on 10-kg increments in weight.

The impact of self-administration on efficacy was evaluated by assessing PASI response in subjects who self-administered versus healthcare professional administration of CNTO 1275 (STELARA, ustekinumab) at Week 16.

The hospital anxiety and depression scale and work limitations questionnaire were also used to assess patient reported outcomes.

Improvements in quality of life were also assessed by the Hospital Anxiety and Depression Scale (HADS) and the Work Limitations Questionnaire (WLQ).

The impact of CNTO 1275 (STELARA, ustekinumab) on health economics measures was assessed by measuring employment status, the number of work days missed due to psoriasis, and the change from baseline in subjects' reported productivity.

#### *Sample size*

Study PHOENIX 1: A total of 984 subjects were screened and 766 subjects were randomized to treatment. All 255 subjects randomized to 45 mg received at least 1 dose of 45 mg and 255 of 256 subjects randomized to 90 mg received at least one dose of 90 mg. Of the 255 subjects randomized to placebo, all subjects received placebo at Week 0. At Week 12, 123 (96.9%) of the 127 placebo subjects randomized to Group 3a crossed over to 45 mg, and 120 (93.8%) of the 128 placebo subjects randomized to Group 3b crossed over to 90 mg.

The safety population through the end of the reporting period, therefore included:

- 255 subjects treated with placebo through Week 12
- 123 subjects in the placebo → 45 mg group
- 120 subjects in the placebo → 90 mg group
- 255 subjects in the 45 mg group
- 255 subjects in the 90 mg group.

Study PHOENIX 2: A total of 1567 subjects were screened, and 1230 subjects were randomized to treatment. All randomized subjects received treatment in the study. The safety population through Week 28, therefore included:

- 410 subjects treated with placebo through Week 12
- 197 subjects in the placebo → 45 mg group
- 195 subjects in the placebo → 90 mg group
- 409 subjects in the 45 mg group
- 411 subjects in the 90 mg group.

#### *Randomisation*

Both study PHOENIX 1 and study PHOENIX 2: Subject allocation to a treatment group at Week 0 (or Week 40 for study PHOENIX 1) was performed using a centralized IVRS provided by Clinphone. Subjects were randomized to a treatment group using a minimization algorithm with a biased coin assignment (Pocock and Simon, 1975).

At Week 0, eligible subjects were randomized to 1 of 3 treatment groups as follows:

Group 1: ustekinumab 45 mg at Weeks 0 and 4 followed by 45 mg q12w;

Group 2: ustekinumab 90 mg at Weeks 0 and 4 followed by 90 mg q12w;

Group 3: Placebo at Weeks 0 and 4 (half the subjects in this group were randomized to

Group 3a at Week 0 to crossover to ustekinumab 45 mg at Weeks 12 and 16, and half were randomized to Group 3b at Week 0 to crossover to ustekinumab 90 mg at Weeks 12 and 16).

The randomization at Week 0 was stratified by investigational site, weight ( $\leq 90$  kg or  $> 90$  kg), and whether there were  $< 3$  or  $\geq 3$  conventional therapies (ie, psoralen plusultraviolet A light [PUVA], methotrexate [MTX], acitretin, and cyclosporine) to which the subject had an inadequate response, intolerance, or contraindication.

#### *Blinding (masking)*

Study PHOENIX 1: To maintain the blind associated with CNTO 1275 (STELARA, ustekinumab) dose administration, each subject randomized to CNTO 1275 (STELARA, ustekinumab) was also given a placebo injection; subjects in the 45 mg group received a 1.0 mL placebo injection, and subjects receiving 90 mg also received a 0.5 mL placebo injection. Two lots of placebo (D05PE7429 and D05PE7430) were used. The site monitors, investigators, and site personnel associated with the conduct of the study, and subjects in the study were to be blinded to treatment assignment until the Week 76 database is finalized and locked. To maintain the blind, all administrations were to be given as 2 SC injections, 1 syringe containing 0.5 mL and 1 syringe containing 1.0 mL of study agent. Unblinding of treatment information for individual subjects was allowed for specific safety reasons and required a request from the investigator on an individual subject basis. To receive the treatment group assignment of a specific subject, an investigator had to contact the Centocor medical monitor or designee.

Study PHOENIX 2: At the Week 28 database lock, the treatment assignment at Week 0 was unblinded to the Sponsor for analysis while subjects were still being followed in the study. The site monitors, investigators, site personnel associated with the conduct of the study and subjects in the study are to be blinded to treatment assignment until the Week 52 database is locked and finalized. To maintain the blind, all administrations were to be given as 2 SC injections, 1 syringe containing 0.5 mL and 1 syringe containing 1.0 mL of study agent. Emergency unblinding is performed as for PHOENIX 1.

#### *Statistical methods*

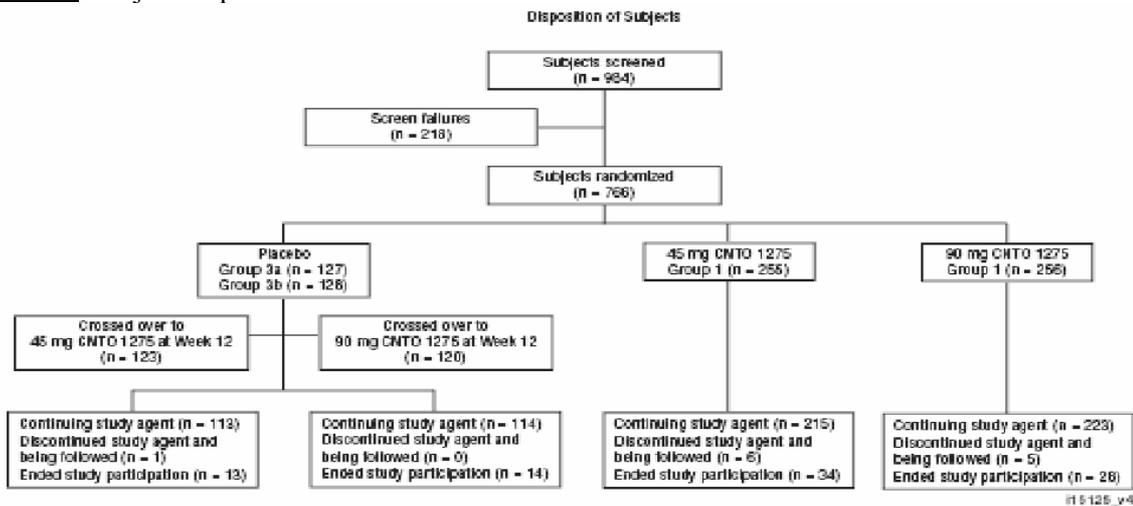
Subject allocation to treatment group used a minimisation algorithm with stratification factors of weight ( $\leq 90$  kg or  $> 90$  kg) and the number of previous therapies to which the patient had been exposed or was intolerant to.

The applicant measured PASI75 responders at week 12, as well as PGA responders at week 12. The difference in responder proportions between each level of ustekinumab and placebo was calculated and 95% confidence intervals presented. PASI90 responder rates and PASI50 responder rates were also provided. Missing data was handled using last observation carried forward (LOCF). The applicant provided 3 different methods for handling missing data to test the sensitivity of using LOCF: a per-protocol population, a method assuming all missing data are failures, and a method based on linear interpolation of results.

## RESULTS

### Participants flow

#### PHOENIX 1: subject disposition at week 0 randomization.

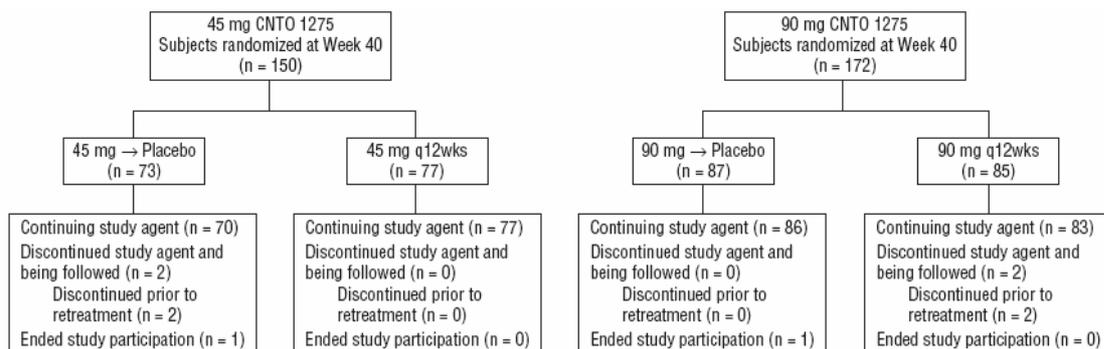


**Figure 2** Subject disposition through the date the last subject completed Week 52; subjects randomized at Week 0

The most common reason for discontinuation in the ustekinumab groups was Other (7 [1.4%]), including 1 (0.4%) subject in the 45 mg group who discontinued study agent after requiring use of a prohibited medication, and 6 (2.3%) subjects in the 90 mg group, 3 who were discontinued after randomization because they were in violation of eligibility criteria, 2 who discontinued because they moved and were no longer able to participate in the study, and 1 who was discontinued due to non-compliance.

In the placebo group, the most common reason for discontinuation of study agent was an AE (6 [2.4%]). Notably, 6 subjects in the placebo group discontinued study agent due to a lack of improvement of psoriasis, (3 [1.2%] subjects had an AE of worsening of psoriasis and 3 [1.2%] had unsatisfactory therapeutic effect), compared with no subjects treated with 45 mg and 1 [0.2%] subject treated with 90 mg who had unsatisfactory therapeutic effect.

#### PHOENIX 1: subject disposition at week 40 randomization.



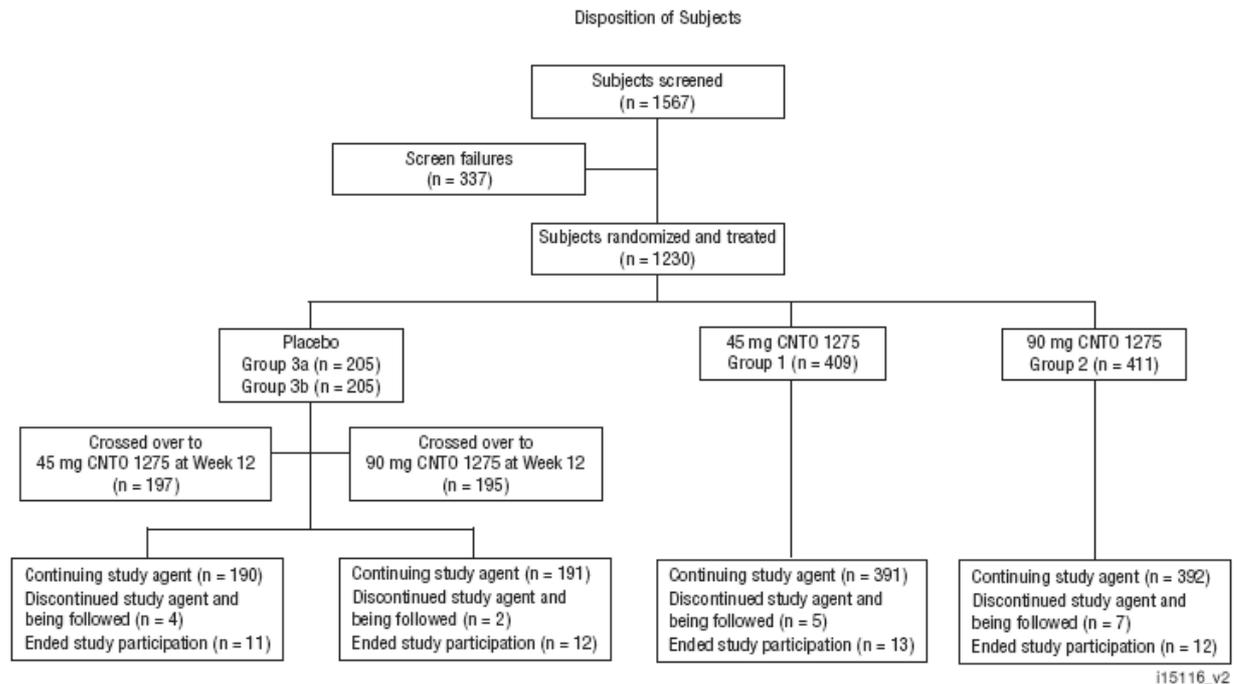
A total of 100 (13.1%) subjects permanently discontinued study agent administration through the end of the reporting period.

A greater proportion of subjects discontinued study agent in the 45 mg group than in the 90 mg group (40 [15.7%] and 32 [12.5%], respectively). This small disparity was attributable to a greater proportion of subjects discontinuing therapy at Week 28 in the 45 mg group because they were non-responders and discontinued per protocol (i.e. Landmark visit (Week 28) non-responder per protocol; 17 [6.7%] subjects in the 45 mg group compared with 5 [2.0%] in the 90 mg group). The proportion of subjects discontinuing study agent was similar in the placebo → 45 mg group and placebo → 90 mg group (14

[11.0%] and 14 [10.9%], respectively). Of note, the placebo → 45 mg and the placebo → 90 mg columns included discontinuations during the placebo period (i.e. through Week 12). The most frequent reason for discontinuation of study agent administration for all treatment groups combined was AEs (4.3%). Generally similar proportions of subjects discontinued study agent due to AEs in all treatment groups.

A total of 25 (3.3%) subjects among all treatment groups recorded “other” as reason for discontinuation of study agent administration through the end of the reporting period. The most common responses for the “other” category included noncompliance with the protocol. Subjects who discontinued due to an AE of worsening psoriasis or unsatisfactory therapeutic effect were counted as treatment failures.

## PHOENIX 2:



In PHOENIX 2 a total of 66 (5.4%) subjects permanently discontinued study agent administration through Week 28, as shown in Table 4. The proportion of subjects discontinuing study agent was similar in the 45 mg and 90 mg groups (18 [4.4%] and 19 [4.6%], respectively). The proportion of subjects discontinuing study agent was also similar in the placebo → 45 mg group and the placebo → 90 mg group (15 [7.3%] and 14 [6.8%], respectively). Of note, the placebo → 45 mg and the placebo → 90 mg columns included discontinuations during the placebo-controlled period (i.e. through Week 12). The most frequent reason for discontinuation of study agent administration for all treatment groups combined was AEs. Generally similar proportions of subjects discontinued study agent due to AEs in all treatment groups. A total of 21 (1.7%) subjects among all treatment groups recorded “other” as reason for discontinuation and the most common responses for the “other” category included non-compliance with the protocol.

### Conduct of the study

To ensure balance across treatment arms, a minimisation algorithm with a biased coin design was used, to ensure balance across weight ( $\leq 90$  kg or  $> 90$  kg) and the number of systemic therapies each patient had failed ( $< 3$  or  $\geq 3$ ).

### Baseline data

Baseline disease characteristics were well matched in all studies. After randomization demographics and disease characteristics were well matched between groups.

### Numbers analysed

The numbers analysed were sufficient to demonstrate strong statistical and clinical significance for the superiority of ustekinumab over placebo for the treatment of psoriasis.

#### *Outcomes and estimation*

PASI 75, PGA and DLQI were most common measures of disease response in all trials. Efficacy measures were incorporated into the Phase 3 studies to evaluate the impact of CNTO 1275 (STELARA, ustekinumab) on skin and nail psoriasis, on itch, on quality of life, and on health economics. All aspects of psoriasis were evaluated by standard assessments that are all well accepted. Additionally, quality of life assessments allowed a measure of efficacy from the subject's perspective.

- Measures of skin psoriasis in both PHOENIX 1 and PHOENIX 2 included PASI and the static PGA (of disease severity);

- Nail psoriasis was measured in PHOENIX 1 using the Nail Psoriasis Severity Index (NAPSI), a Nail PGA, and the number of nails involved by psoriasis;

- Itch was measured in PHOENIX 1 by a visual analog scale (itch VAS);

DLQI score was evaluated in both studies as a measure of the impact of CNTO 1275 (STELARA, ustekinumab) treatment on quality of life. Additionally, the SF-36 was used to evaluate quality of life in PHOENIX 1, and the Hospital Anxiety and Depression Scale (HADS) and the Work Limitations Questionnaire (WLQ) were used to evaluate quality of life in PHOENIX 2. Health economic assessments were evaluated in both studies using measures of subjects' employment status, time lost from work, and daily productivity.

#### Study PHOENIX 1:

Information on the efficacy of ustekinumab is provided in 3 of the 4 study periods in PHOENIX 1 – the placebo-controlled period (Weeks 0-12), the active treatment period (Weeks 12-40 when all subjects received CNTO 1275), and the randomized withdrawal period (Week 40 through the end of the reporting period). Since data were collected through the date the last subject completed the Week 52 visit, a small amount of data after Week 52 are included (during the long-term extension period).

There was significant improvement in the PASI 75, PASI 90 and PGA of the two treatment groups compared with placebo over the first 12 weeks.

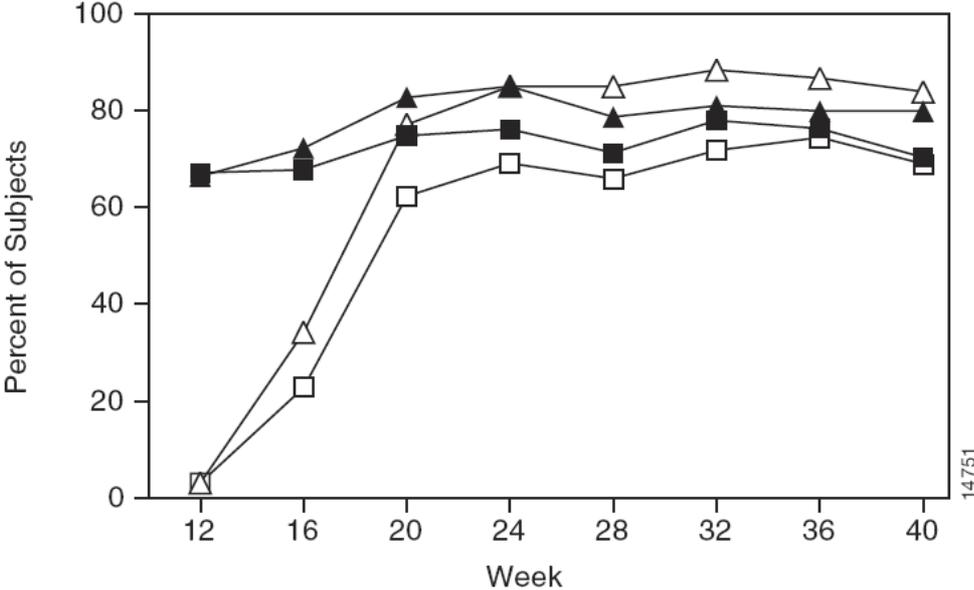
There was very strong statistical evidence for the superiority of CNTO 1275 (STELARA, ustekinumab) over placebo for the treatment of psoriasis as measured by PASI 75. There was no evidence of an important difference between the 2 doses at this 12 week time-point.

The applicant also provided 3 sensitivity analyses to assess the impact of using LOCF to handle the missing data, the most conservative of which was to assume all missing data were treatment failures. The results for this were identical to the ones above, as the last observation of all missing individuals was one of treatment failure.

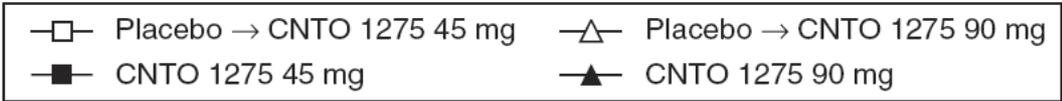
Dose response separation began to emerge at Week 16, when 72.2% of subjects in the 90 mg group achieved a PASI 75 response compared with 67.7% of subjects in the 45 mg group. This separation in response rates peaked at approximately 24 weeks and generally persisted through Week 40 (the last timepoint before the randomized withdrawal portion of the study).

To evaluate longer term efficacy, psoriasis improvement was assessed over time by PASI from Week 12 through Week 40, after the placebo group crossed over to CNTO 1275 (STELARA, ustekinumab) (Figure 3).

**Figure 3 PHOENIX 1. Percent of subjects achieving PASI 75 response from Week 12 through Week 40 by visit; subjects randomized at Week 0**

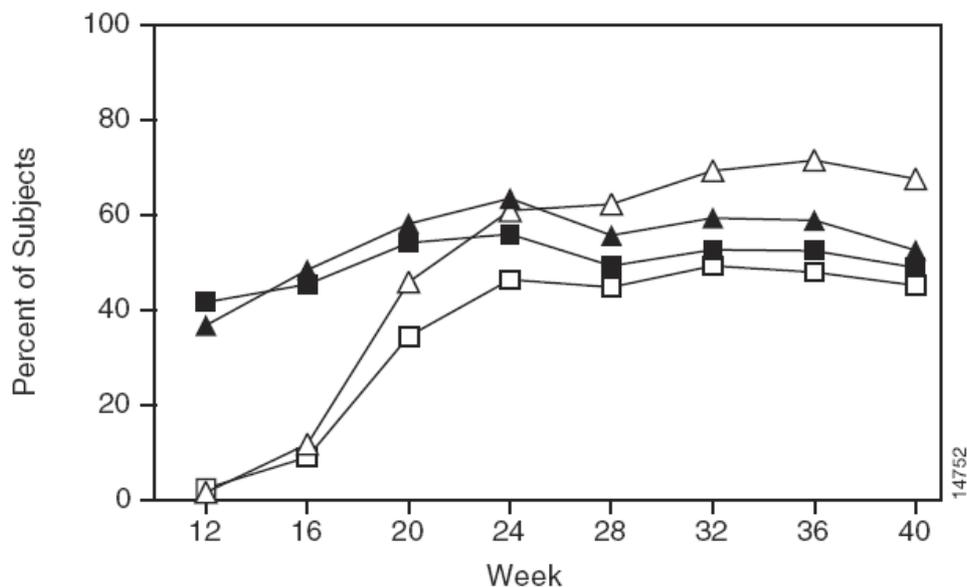


Placebo → 45 mg	n = 127	123	122	123	123	120	121	122
Placebo → 90 mg	n = 128	120	118	120	119	120	119	117
CNTO 1275 45 mg	n = 255	254	250	251	250	249	248	246
CNTO 1275 90 mg	n = 256	248	248	246	243	241	238	238

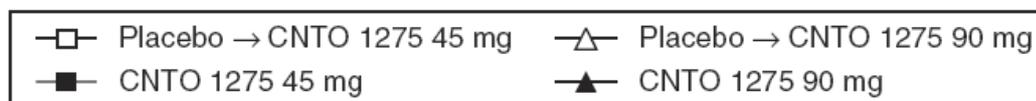


The majority of subjects achieved a PASI 90 response with response rates observed around Week 24 in both the 45 mg (55.8%) and 90 mg (63.4%) groups (see Figure 15). The periodicity of response, i.e., the slightly higher response rates 4 and 8 weeks post dose compared with the 12 weeks post dose response, was also observed with PASI 90 responses but was not apparent with PASI 50 responses, which remained generally stable after reaching their maximum.

**Figure 15 Percent of subjects achieving PASI 90 response from Week 12 through Week 40 by visit; subjects randomized at Week 0.**



Placebo → 45 mg	n = 127	123	122	123	123	120	121	122
Placebo → 90 mg	n = 128	120	118	120	119	120	119	117
CNTO 1275 45 mg	n = 255	254	250	251	250	249	248	246
CNTO 1275 90 mg	n = 256	248	248	246	243	241	238	238



*Impact of CNTO 1275 (STELARA, ustekinumab) on Nail Psoriasis*

By Week 12, nail psoriasis was significantly improved in subjects treated with ustekinumab compared with the placebo group as measured by NAPS. The median percent improvement in NAPS from baseline to Week 12 was 25.0% in both ustekinumab groups compared with 0% in the placebo group ( $p < 0.001$  for comparison of the 45 mg group versus the placebo group;  $p = 0.001$  for comparison of the 90 mg group versus the placebo group).

Nail psoriasis showed similar improvements in subjects in the placebo → 45 mg and placebo → 90 mg groups. Combined, these results suggest that the magnitude of improvement in nail psoriasis continued to improve over time through Week 24 and that 45 mg and 90 mg dosing led to a similar magnitude of improvement.

*Impact of CNTO 1275 (STELARA, ustekinumab) on Quality of Life Table 15 Number of subjects with a reduction of 5 or more from baseline in DLQI score at Week 12; subjects randomized at Week 0*

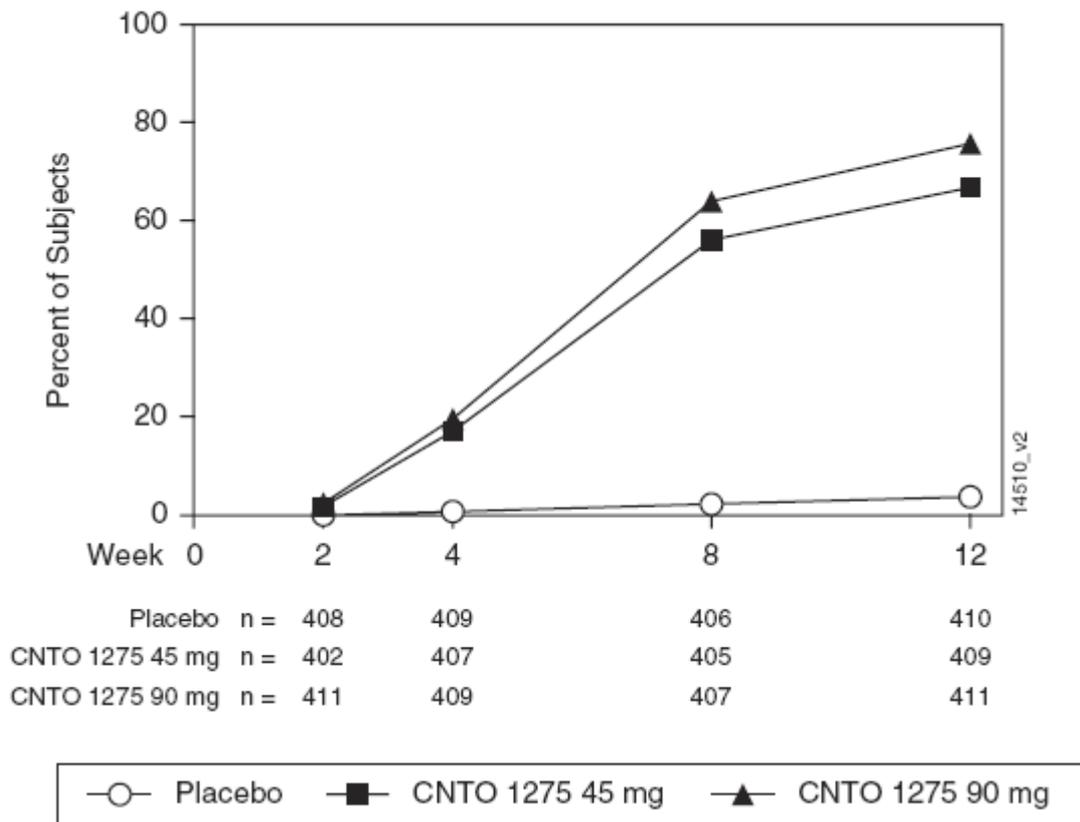
Improvements at Week 12 were sustained at Weeks 28 and 40. Additionally, the placebo → 45 mg and placebo → 90 mg groups had improvements in DLQI score at Weeks 28 and 40 that were similar in magnitude to those seen in subjects initially randomized to ustekinumab. During the randomized withdrawal period, DLQI score improvements observed at Week 40 were generally sustained at Week 52 in subjects randomized to maintenance therapy. In contrast, the improvement in DLQI score was lower at Week 52 (compared with Week 40) in subjects withdrawn from ustekinumab, indicating impairment in QOL after 1 missed ustekinumab dose.

No notable between-group differences were observed for employment status. In both ustekinumab groups treatment resulted in a reduction in the number of work days missed due to psoriasis at Week 12.

Study PHOENIX 2:

Study PHOENIX 2 enrolled 1230 subjects and the randomization of subjects to treatment was stratified based on investigational site, weight ( $\leq 90$  kg or  $> 90$  kg), and previous experience with conventional systemic therapies (inadequate response to, intolerance to, or contraindication to  $< 3$  or  $\geq 3$  conventional systemic therapies including cyclosporine, MTX, acitretin, and PUVA). As in PHOENIX 1, it was estimated that approximately 10% of subjects would have had an inadequate response to, intolerance to, or contraindication to  $\geq 3$  conventional systemic therapies, and since PHOENIX 2 was even larger than PHOENIX 1, the study was also adequately powered to demonstrate efficacy in this subpopulation.

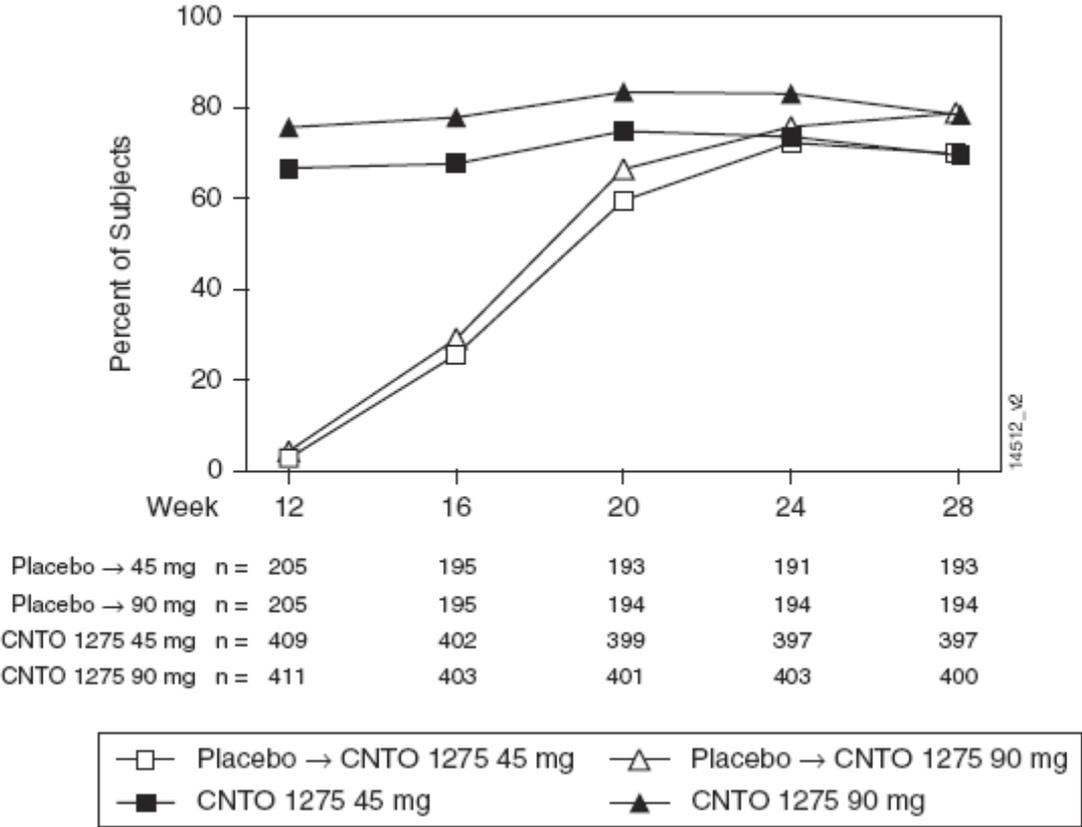
**Figure 5 Percent of subjects achieving PASI 75 response through Week 12 by visit; subjects randomized at Week 0 in PHOENIX 2.**



Patterns of efficacy over time from Week 12 through Week 28 were generally similar when measured by different PASI thresholds, by PGA, and by continuous measures of response (e.g. median percent PASI improvement) though magnitude of response varied according to the threshold.

Efficacy with ustekinumab 1275 continued to improve after the placebo-controlled portion of the study

**Figure 6 Percent of subjects achieving PASI 75 response from Week 12 through Week 28 by visit; subjects randomized at Week 0 in PHOENIX 2**



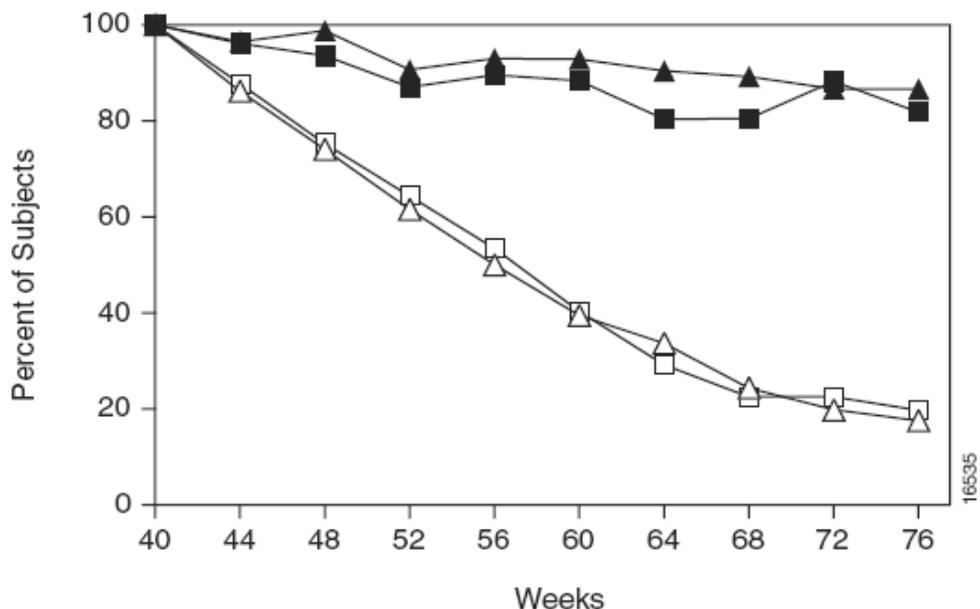
Clinical response (improvement in PASI) was related to serum ustekinumab levels. Subjects treated with ustekinumab demonstrated significant improvements in quality of life that generally paralleled their PASI responses. Significant improvements in DLQI scores were noted as early as Week 4 in each ustekinumab group compared with placebo and continued to improve at Week 12.

An analysis of efficacy over time from Week 16 through Week 28 showed that PASI response rates were similar in subjects self-administering ustekinumab and in those in whom ustekinumab was administered by a healthcare professional.

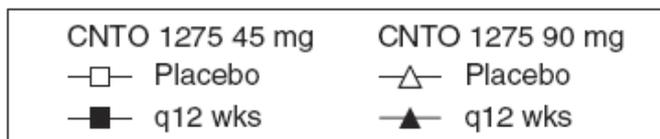
Both Study PHOENIX 1 and Study PHOENIX 2 demonstrate the superiority of ustekinumab over placebo in the treatment of plaque psoriasis when measured by PASI, PGA and QOL readouts. Efficacy was shown for adult patients with psoriasis with PASI, PGA and DLQ index scores when compared with placebo. With long-term treatment (up to 40 weeks) the response was durable. There was some evidence of the efficacy of re-treatment in subjects who lost 50% of their PASI response on discontinuing therapy in PHOENIX 1.

**Long-term efficacy and efficacy of re-treatment**

During the procedure the Applicant provided the week 76 CSR for PHOENIX 1. The data from this demonstrated that efficacy is maintained through week 76 (See Figure 5).



CNTO 1275 45 mg										
Placebo n = 73	73	73	73	73	72	72	71	71	71	71
q12 wks n = 77	77	77	77	77	77	76	77	76	77	77
CNTO 1275 90 mg										
Placebo n = 87	87	85	86	86	86	86	86	86	86	85
q12 wks n = 85	85	85	85	84	83	83	83	83	83	82



**Figure 5** Percent of subjects achieving PASI 75 response from Week 40 through Week 76 by visit; subjects randomized at Week 40

The efficacy of re-treatment was assessed and this was evident whether measured by PASI, PGA or DLQI. (Attachment 3.11 below), as was relapse within 8 weeks on withdrawal of therapy.

**Attachment 3.11 Summary of PASI 75 responders following the reinitiation of CNTO 1275; subjects withdrawn from CNTO 1275 at Week 40**

	CNTO 1275				
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg	Combined
Subjects withdrawn from CNTO 1275 at Week 40	68	92	73	87	320
Subjects retreated	43	54	45	53	195
Subjects evaluated after retreatment	43	54	45	53	195
≥ 75% improvement at any time after retreatment	37 (86.0%)	43 (79.6%)	37 (82.2%)	50 (94.3%)	167 (85.6%)
Subjects evaluated 4 weeks after retreatment	43	54	45	53	195
≥ 75% improvement 4 weeks after retreatment	12 (27.9%)	21 (38.9%)	14 (31.1%)	16 (30.2%)	63 (32.3%)
Subjects evaluated 8 weeks after retreatment	37	49	41	50	177
≥ 75% improvement 8 weeks after retreatment	24 (64.9%)	33 (67.3%)	30 (73.2%)	39 (78.0%)	126 (71.2%)
Subjects evaluated 12 weeks after retreatment	34	42	34	42	152
≥ 75% improvement 12 weeks after retreatment	29 (85.3%)	35 (83.3%)	27 (79.4%)	38 (90.5%)	129 (84.9%)

RE260.[E\_PASI\_81\_A].26OCT2007 15:39

*Active comparator trial*

The Applicant provided the week 12 CSR for ACCEPT is a multicenter (67 sites), randomized, active-controlled, parallel, 3-arm study of SC injections of ustekinumab 45 mg, ustekinumab 90 mg, and etanercept 50 mg (twice weekly) in subjects with moderate to severe psoriasis. The active-controlled portion of the study was from Week 0 to Week 12, during which the efficacy and safety of etanercept and ustekinumab 45 mg and 90 mg were evaluated. The second part of the study, beginning at Week 12, will evaluate interruption of therapy and re-treatment. Treatment after Week 12 is dependent on PGA response at Week 12 and initial treatment assignment. The final (Week 64) CSR will be available mid-2009.

The data provided with this trial demonstrated that ustekinumab was superior to etanercept.

**Table 9** Number of PASI 75 responders at Week 12; subjects in the combined ustekinumab group (weight-based) or randomized to etanercept

	Etanercept	Ustekinumab		Combined
		45 mg	90 mg	
Subjects in the combined ustekinumab group (weight-based) or randomized to etanercept <sup>a</sup>	347	151	103	254
PASI 75 responders	197 (56.8%)	109 (72.2%)	67 (65.0%)	176 (69.3%)
p-value <sup>b</sup>				0.002

<sup>a</sup> The combined ustekinumab group (weight-based) is composed of subjects randomized to ustekinumab 45 mg and with baseline weight ≤ 100 kg and of subjects randomized to ustekinumab 90 mg and with baseline weight > 100 kg.

<sup>b</sup> The p-value is for comparing the PASI 75 response rates of the combined ustekinumab group and the etanercept group.

RE300[E\_PASI\_111\_A]. 22FEB2008 14:58

#### Ancillary analyses

- Analysis performed across trials (pooled analyses and meta-analysis)

Cross-study comparisons of efficacy focused on comparing results from the Phase 3 studies where the same dosing regimens were used. The Phase 3 study designs were identical for 28 weeks, so the comparisons are limited to this time period. Cross-study comparisons focused on evaluating consistency in:

- The magnitude of treatment effect versus placebo;
- Dose-response in efficacy;
- Time to onset of efficacy and response over time.

For subgroups defined by the following variables, data were pooled from the Phase 3 (PHOENIX 1 and PHOENIX 2) studies to provide a more precise estimate of efficacy:

- Age (< 45 years, ≥ 45 to < 65 years, ≥ 65 years);
- BMI (Normal [ $< 25$ ], overweight [ $\geq 25$  to  $< 30$ ], obese [ $\geq 30$ ]);
- Prior exposure to phototherapy (UVB or PUVA), conventional systemics (PUVA, MTX, acitretin, or cyclosporine) or biologics (etanercept, alefacept, efalizumab, infliximab, or adalimumab);
- Prior experience with conventional antipsoriatic systemic therapies (inadequate response to, were intolerant to, or had at a contraindication to PUVA, MTX, acitretin, or cyclosporine). Similar trends in efficacy were observed in these subpopulations in both Phase 3 studies, supporting the use of pooled data to provide a more precise estimate of treatment effect.

Demographics and baseline disease characteristics and previous use of systemic therapy for psoriasis were similar between the two phase 3 trials.

The primary endpoint of both PHOENIX 1 and PHOENIX 2 examined the proportions of subjects achieving PASI 75 response at Week 12, and the first major secondary endpoint in each trial examined the proportions of subjects with a PGA score of cleared or minimal at Week 12.

The studies showed significant and reproducible improvements in psoriasis at Week 12 using either PASI or PGA response.

The Phase 3 studies, which studied identical dosing regimens, met the primary and all major secondary endpoints and showed remarkable consistency in the magnitude of effect by Week 28. A dose response in efficacy was observed in PHOENIX 2, with approximately 10% difference in efficacy observed between the 45 and 90 mg groups, though similar differences were not observed in PHOENIX 1. Results of PHOENIX 2 are most consistent with previous observations in Phase 2, in

which approximately 10% increments in PASI 75 response were observed with every doubling in exposure between 45 mg and 360 mg.

Both PHOENIX 1 and PHOENIX 2 showed rapid onset of action of CNTO 1275, with approximately 10% of subjects in the 45 mg and 90 mg groups achieving a PASI 50 response by Week 2. The rapid and clinically significant improvements in psoriasis in both groups continued to increase over time, both in the proportions of responding subjects as well as in the magnitude of their response, through the primary study endpoint at Week 12. Approximately 35 to 50% of subjects achieved a PASI 90 response at Week 12. Similar efficacy with CNTO 1275 (STELARA, ustekinumab) treatment was observed when efficacy was assessed using the PGA.

Across PHOENIX 1 and PHOENIX 2, the relationship of antibodies to efficacy was consistent in that subject's positive for antibodies tended to have lower efficacy.

A significant proportion of subjects randomized to CNTO 1275 (STELARA, ustekinumab) (approximately 36% from PHOENIX 1 and PHOENIX 2 combined) achieved a DLQI score of 0 (ie, no detectable impairment in quality of life) at Week 12. Similarly, a high proportion of subjects achieved a reduction of 5 or more points in DLQI score at Week 12, which corresponds to a clinically important difference

Subgroup analysis of subjects with diabetes, weight, psoriasis medication history and demographics were consistent between the two trials. The magnitude of the treatment effect was slightly lower in subjects who were  $\geq 65$  years or subjects who were obese (BMI  $\geq 30$ ), though still significant and substantial. For subjects who were  $\geq 65$  years of age, a slightly lower treatment effect was observed in the 90 mg group, which was also observed in PHOENIX 2. Since the number of subjects  $>75$  of age was limited in the Phase 3 studies (n = 11), efficacy analyses were not performed on this subgroup.

- Clinical studies in special populations

Consistency of CNTO 1275 (STELARA, ustekinumab) efficacy across relevant subpopulations was also evaluated in each Phase 3 study. Most of the subgroups evaluated were large enough to provide robust assessments within each of the individual Phase 3 studies. In particular, each study was adequately powered to demonstrate efficacy in a more restricted patient population of subjects who had an inadequate response to, were intolerant to, or had a contraindication to conventional systemic therapies including cyclosporine, methotrexate (MTX), acitretin, or psoralen plus ultraviolet A light (PUVA).

In the individual Phase 3 studies, efficacy was evaluated in subpopulations based on:

- Gender, race, and age.
- Geographic region.
- Duration of disease.
- Age at diagnosis.
- Body Mass Index (BMI) and weight.
- Disease severity including moderate and severe psoriasis (see below).
- Presence or absence of PsA as a comorbidity.
- Prior exposure to conventional systemic therapies, phototherapy, and biologics (etanercept, alefacept, efalizumab, infliximab, or adalimumab).
- Prior experience with conventional systemic therapies (inadequate response to, were intolerant to, or had a contraindication to PUVA, MTX, acitretin, or cyclosporine).
- Prior experience with biologics (inadequate response to or were intolerant to etanercept, alefacept, efalizumab, infliximab, or adalimumab).

The main findings from analysis of these subpopulations was that:

- There is consistently very strong statistical evidence for the superiority of CNTO 1275 (STELARA, ustekinumab) over placebo, including in those who had an inadequate response, were intolerant, or were contraindicated to at least 3 conventional systemic therapies, both for the 45 mg and 90 mg doses. There is evidence of a dose response effect in both studies in this subgroup. In PHOENIX 2, this mirrors what happens in the overall population, whereas in PHOENIX 1, no overall difference was seen between the 2 doses in patients failing two therapies or fewer.
- 90mg was more effective in patients over 100kg.

### Impact of Weight on Psoriasis Improvement

The results of the subgroup analysis by weight are shown below, using both a 90 kg cut-off point and a 100 kg cut-off point:

#### PHOENIX 1:

	Placebo		45 mg		90 mg	
90kg	N	Responders (%)	N	Responders (%)	N	Responders (%)
<90	120	6 (5.0%)	120	94 (77.7%)	121	81 (66.9%)
>90	135	2 (1.5%)	134	77 (57.5%)	134	89 (65.9%)
100kg						
<100	166	6 (3.6%)	168	124 (73.8%)	164	107 (65.2%)
>100	89	2 (2.2%)	97	47 (54.0%)	92	63 (68.5%)

#### PHOENIX 2:

	Placebo		45 mg		90 mg	
90kg	N	Responders (%)	N	Responders (%)	N	Responders (%)
<90	216	9 (4.2%)	222	161 (72.5%)	219	173 (79.0%)
>90	194	6 (3.1%)	187	112 (59.9%)	191	138 (72.3%)
100kg						
<100	290	12 (4.1%)	297	218 (73.4%)	289	225 (77.9%)
>100	120	3 (2.5%)	112	55 (49.1%)	121	86 (71.1%)

#### T04 - Phase II study

(The applicant presents the response rates by weight, using 95kg as a cut-off value to define the 2 categories)

	Placebo	45 mg (single dose)	90 mg (single dose)	45 mg (weekly ×4)	90 mg (weekly ×4)
<95 kg	1 (2.4%)	27 (65.9%)	28 (66.7%)	28 (70.0%)	34 (82.9%)
>95 kg	0 (0.0%)	6 (26.1%)	10 (45.5%)	15 (62.5%)	18 (78.3%)

- Supportive study(ies)

Supportive studies included the trial on psoriatic arthritis (which showed moderate efficacy in PsA), and that on Multiple Sclerosis patients (provided additional pharmacodynamic immune system). Patients from these trials and others contributed to the safety data provided by the Applicant in the day 120 Safety update Report.

A controlled trial (C0743T12) of 12 weeks data was presented, which supported superiority of Stelara over etanercept in terms of PASI responses and PGA at 12 weeks.

The primary objectives of this study were to compare the efficacy of ustekinumab to etanercept and evaluate the safety of ustekinumab and etanercept. The secondary objective is to evaluate the efficacy and safety of retreatment with ustekinumab.

This was a Phase 3 multicenter, randomized, active-controlled, parallel, 3-arm study of SC injections of ustekinumab 45 mg at Weeks 0 and 4, ustekinumab 90 mg at Weeks 0 and 4, and etanercept 50 mg twice weekly through Week 12 in subjects with moderate to severe plaque psoriasis. 903 subjects were randomized to ustekinumab 45 mg, ustekinumab 90 mg, or etanercept 50 mg in a 3:5:5 ratio. Subjects were randomized in a 3:5:5 ratio to 1 of 3 treatment groups as follows:

Group 1: ustekinumab 45 mg at Weeks 0 and 4.

Group 2: ustekinumab 90 mg at Weeks 0 and 4.

Group 3: etanercept 50 mg twice weekly through Week 12.

This study revealed that in subjects with moderate to severe plaque psoriasis, ustekinumab 45 mg and 90 mg have superior efficacy to etanercept 50 mg as measured by PASI and PGA. In addition, ustekinumab therapy was generally well tolerated through Week 12, with an overall safety profile comparable to etanercept.

- **Discussion on clinical efficacy**

The efficacy of Stelara in PASI (Psoriasis Area and Severity Index), PGA (Physician's Global Assessment) and DLQI (Dermatology Life Quality Index) scores was statistically significantly superior to placebo and etanercept in plaque psoriasis after 12 weeks of treatment. The proportion of patients achieving PASI 75 response at week 12 was 72.2% and 65% on 45 mg and 90 mg respectively versus 56.8% on etanercept. Approximately 35 to 50% of subjects achieved a PASI 90 response at week 12. Similar efficacy with Stelara treatment was observed when efficacy was assessed using the PGA.

The lack of a comparator was noted in the initially submitted dose-response studies. The effect was delayed taking >6 weeks to achieve maximal effect, was weight and dose dependent, long-lasting (up to 12 weeks) and re-treatment was effective in those who did not respond initially. Subjects with weight >100kg had less response to the lower dose than did lighter subjects.

- **Clinical safety**

To evaluate the safety of ustekinumab, AEs and laboratory assessments were systematically captured in each clinical study and categorized by the investigator for seriousness, intensity, causality (assessed by the investigator), duration, and action taken with study drug. These AEs were then organized by system-organ class and preferred term using the MedDRA dictionary. Safety events particularly relevant in the psoriasis population were also evaluated, such as psoriasis rebound and flares of psoriatic arthritis. Additionally, targeted analyses were conducted to evaluate the impact of ustekinumab on other comorbidities (eg, hypertension, obesity, and diabetes), and its impact on the rates of nonserious and serious cardiovascular events, death and hospitalization in the clinical study population compared with the rates observed in the general and/or psoriasis population.

AEs that were classified separately were infections, infections treated with oral or parenteral antibiotics and injection site reactions. Routine hematology and chemistry laboratory parameters were captured at selected time-points during each study. Additionally, tests on Subsets of lymphocytes, Electrocardiograms (ECGs) and Immune responses to vaccines were examined in the Phase 1 studies to assess immunocompetency. D-dimer levels were obtained at baseline and Week 12 in the Phase 3 studies as a surrogate marker of occult thrombosis, C-reactive protein (CRP) levels were obtained at baseline and Week 12 as a surrogate marker of cardiovascular risk, Fasting glucose levels were examined at baseline and Week 12 in Phase 3 to evaluate the impact of ustekinumab on diabetes and Hemoglobin A1c levels were obtained at baseline and Weeks 12, 24, 36, and 52 in Phase 3 to evaluate the impact of ustekinumab on glucose homeostasis over time.

- **Patient exposure**

The safety database in the original application was deemed too small for an agent which blocks two cytokines and is proposed for use in a non life-threatening indication. In addition, from the data available in the original application the safety profile seemed similar to placebo over a 12-week period but no longer term comparator group nor an active comparator group were present. During the procedure the Applicant provided significantly more safety data and the week 12 CSR of the ACCEPT trial where ustekinumab was compared with etanercept.

This additional data provided approximately 50% more safety follow-up in the 2266 ustekinumab-treated subjects in the psoriasis Phase 2 and Phase 3 studies. As shown in Table 29-3, a total of 1970 subjects were exposed for at least 6 months (an additional 368 since the initial MAA), 1285 subjects were exposed for at least 1 year (an additional 923), and 373 subjects were exposed for at least 18 months.

**Table 29-2 Summary of duration of ustekinumab exposure and total ustekinumab dose through the initial MAA cutoff; subjects treated with ustekinumab in psoriasis Phase 2 and Phase 3**

	Ustekinumab		
	45 mg	90 mg	Combined
Subjects treated with ustekinumab	1110	1156	2266
Duration of ustekinumab exposure			
At least 6 months <sup>a</sup>	812 (73.2%)	790 (68.3%)	1602 (70.7%)
At least 1 year <sup>b</sup>	191 (17.2%)	171 (14.8%)	362 (16.0%)
Avg number of ustekinumab administrations	3.4	3.2	3.3
Total dose (mg) <sup>c</sup>			
n	1110	1156	2266
Mean ± SD	153.0 ± 64.73	288.7 ± 129.28	222.2 ± 123.21
Median	135.0	270.0	180.0
IQ range	(90.0, 180.0)	(180.0, 360.0)	(135.0, 270.0)
Range	(45, 360)	(45, 720)	(45, 720)

<sup>a</sup> The duration between the first and last ustekinumab administration was at least 14 weeks.

<sup>b</sup> The duration between the first and last ustekinumab administration was at least 38 weeks.

<sup>c</sup> Partial injections are counted as full injections.

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**Table 29-3 Summary of duration of ustekinumab exposure and total ustekinumab dose through the 120-day Safety Update Report cutoff; subjects treated with ustekinumab in psoriasis Phase 2 and Phase 3**

	Ustekinumab		
	45 mg	90 mg	Combined
Subjects treated with ustekinumab	1110	1156	2266
Duration of ustekinumab exposure			
At least 6 months <sup>a</sup>	994 (89.5%)	976 (84.4%)	1970 (86.9%)
At least 1 year <sup>b</sup>	645 (58.1%)	640 (55.4%)	1285 (56.7%)
At least 18 months <sup>c</sup>	187 (16.8%)	186 (16.1%)	373 (16.5%)
Avg number of ustekinumab administrations	5.0	4.7	4.8
Total dose (mg) <sup>d</sup>			
n	1110	1156	2266
Mean ± SD	224.1 ± 81.38	422.1 ± 169.63	325.2 ± 166.48
Median	225.0	450.0	270.0
IQ range	(180.0, 270.0)	(360.0, 450.0)	(225.0, 450.0)
Range	(45, 405)	(45, 900)	(45, 900)

<sup>a</sup> The duration between the first and last ustekinumab administration was at least 14 weeks.

<sup>b</sup> The duration between the first and last ustekinumab administration was at least 38 weeks.

<sup>c</sup> The duration between the first and last ustekinumab administration was at least 62 weeks.

<sup>d</sup> Partial injections are counted as full injections.

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With the additional exposure, 1405 subjects in the psoriasis studies received  $\geq 5$  injections (approximately 1 year of exposure for subjects receiving q12w administration), and 383 received  $\geq 7$  injections (approximately 18 months of exposure for subjects receiving q12w administration), with approximately equal proportions in the 45 mg and 90 mg groups (see Table 29-4).

**Table 29-4 Summary of ustekinumab administrations and total ustekinumab dose through the 120-day Safety Update Report cutoff; subjects treated with ustekinumab in psoriasis Phase 2 and Phase 3**

	Ustekinumab		
	45 mg	90 mg	Combined
Subjects treated with ustekinumab	1110	1156	2266
Number of ustekinumab administrations			
≥ 1	1110 (100.0%)	1156 (100.0%)	2266 (100.0%)
≥ 2	1073 (96.7%)	1062 (91.9%)	2135 (94.2%)
≥ 3	1008 (90.8%)	999 (86.4%)	2007 (88.6%)
≥ 4	924 (83.2%)	926 (80.1%)	1850 (81.6%)
≥ 5	719 (64.8%)	686 (59.3%)	1405 (62.0%)
≥ 6	319 (28.7%)	278 (24.0%)	597 (26.3%)
≥ 7	198 (17.8%)	185 (16.0%)	383 (16.9%)
≥ 8	109 (9.8%)	79 (6.8%)	188 (8.3%)
≥ 9	64 (5.8%)	52 (4.5%)	116 (5.1%)
≥ 10	0 (0.0%)	1 (0.1%)	1 (0.0%)

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Table 29-5 also provides cumulative exposures in subjects receiving q8w administration; 420 subjects were exposed for at least 6 months, 312 subjects were exposed for at least 1 year, and 119 subjects were exposed for at least 18 months

**Table 29-5 Summary of duration of ustekinumab exposure and total ustekinumab dose through the 120-day Safety Update Report cutoff; subjects treated with ustekinumab whose dosing interval was adjusted to q8 weeks at Week 28 or Week 40 in psoriasis Phase 3**

	Ustekinumab		
	45 mg	90 mg	Combined
Subjects treated with ustekinumab whose dosing interval was adjusted to q8 weeks at Week 28 or Week 40	246	174	420
Duration of ustekinumab exposure			
At least 6 months <sup>a</sup>	246 (100.0%)	174 (100.0%)	420 (100.0%)
At least 1 year <sup>b</sup>	180 (73.2%)	132 (75.9%)	312 (74.3%)
At least 18 months <sup>c</sup>	66 (26.8%)	53 (30.5%)	119 (28.3%)
Avg number of administrations	6.9	7.0	6.9
Total dose (mg) <sup>d</sup>			
n	246	174	420
Mean ± SD	309.0 ± 73.33	625.9 ± 147.34	440.3 ± 191.14
Median	270.0	540.0	405.0
IQ range	(225.0, 405.0)	(540.0, 810.0)	(270.0, 540.0)
Range	(180, 405)	(450, 900)	(180, 900)

<sup>a</sup> The duration between the first and last ustekinumab administration was at least 14 weeks.

<sup>b</sup> The duration between the first and last ustekinumab administration was at least 38 weeks.

<sup>c</sup> The duration between the first and last ustekinumab administration was at least 62 weeks.

<sup>d</sup> Partial injections are counted as full injections.

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In addition to the additional data provided for 6 months for both the PHOENIX 1 and PHOENIX 2 trials, the safety of ustekinumab was re-evaluated in data pooled across the Phase 2 and 3 studies in the 120-day Safety Update Report provided by the Applicant.

- **Adverse events**

In the 2 completed Phase 1 studies (C0379T01 and C0379T02), no significant trends were observed in any AEs, which were generally mild. A single SAE (exacerbation of herniated lumbar disc) was reported in C0379T01.

Compared with the short placebo-controlled period (12 weeks) the AEs of infection, malignancy and psychiatric disorders were increased (though not increased with increasing dose) and were similar to the results presented in the week 52 CSR.

The two cases of depression (031-0141 and 109-011) both had a past history of psychiatric disorder (one depression and one bipolar disorder). One subject (020-009) without a history of skin carcinoma or a congenital pre-disposition, with a history of PUVA treatment, developed 10 basal cell carcinomas. He was in the high dose (90mg) group (weight 109kg) and ustekinumab was stopped on day 333 after the 5<sup>th</sup> BCC was identified. While the severe nature of the multiple BCCs in this patient raised concern, he was an isolated case from a large database of patients. Overall there were no new safety signals from the extended data is available from the week 76 CSR of Phoenix 1.

In general, the safety profile was similar across the placebo-controlled Phase 2 (C0379T04) and Phase 3 studies (PHOENIX 1 and PHOENIX 2;). Adverse events were comparable across the placebo and combined CNTO 1275 (STELARA, ustekinumab) treatment groups. No increase in rates of AEs with increased CNTO 1275 (STELARA, ustekinumab) dose was noted. Injections were well tolerated. Rates of antibodies were low and not associated with increased rates of injection-site reactions or serious immunologic events including anaphylaxis or delayed hypersensitivity reactions.

Some notable differences occurred during the placebo-controlled period between the Phase 2 and the Phase 3 studies, particularly with regard to SAEs. SAEs occurred in 3.6% ustekinumab subjects and 1.5% in placebo subjects in Phase 2, whereas SAEs occurred at similar rates in the different treatment groups in both PHOENIX 1 and PHOENIX 2.

During the common placebo-controlled portions (through Week 12) and through to the end of the reporting period of the Phase 2 and 3 studies, the proportions of subjects who had at least 1 AE were comparable among the treatment groups. The proportions of subjects who had at least 1 AE did not increase with dose, and the most frequently reported class of AEs was infections and infestations.

To evaluate the impact of cumulative exposure to ustekinumab on the incidence of AEs, the number of AEs per hundred subject-years of follow-up was evaluated by quartiles of cumulative exposure in the Phase 3 psoriasis studies. Overall, rates of AEs, SAEs, and AEs leading to study agent discontinuation per hundred subject-years of follow-up did not increase with increased exposure.

**Table 7 Number of subjects with 1 or more treatment-emergent adverse events (with frequency of 1% or greater in CNTO 1275-treated subjects) through Week 12 by MedDRA system-organ class and preferred term; treated subjects in psoriasis Phase 2 and Phase 3**

	Placebo	CNTO 1275		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Avg duration of follow-up (weeks)	12.0	12.2	12.1	12.1
Avg exposure (weeks)	4.0	4.0	4.0	4.0
Subjects with 1 or more adverse events	369 (50.4%)	455 (57.6%)	409 (51.6%)	864 (54.6%)
System-organ class/preferred term				
Infections and infestations	168 (23.0%)	210 (26.6%)	199 (25.1%)	409 (25.9%)
Nasopharyngitis	58 (7.9%)	66 (8.4%)	63 (8.0%)	129 (8.2%)
Upper respiratory tract infection	32 (4.4%)	45 (5.7%)	41 (5.2%)	86 (5.4%)
Sinusitis	11 (1.5%)	11 (1.4%)	10 (1.3%)	21 (1.3%)
Gastroenteritis	9 (1.2%)	12 (1.5%)	6 (0.8%)	18 (1.1%)
Influenza	5 (0.7%)	8 (1.0%)	7 (0.9%)	15 (0.9%)
Viral upper respiratory tract infection	2 (0.3%)	8 (1.0%)	5 (0.6%)	13 (0.8%)
Nervous system disorders	58 (7.9%)	74 (9.4%)	78 (9.8%)	152 (9.6%)
Headache	33 (4.5%)	45 (5.7%)	47 (5.9%)	92 (5.8%)
Dizziness	8 (1.1%)	9 (1.1%)	18 (2.3%)	27 (1.7%)
Musculoskeletal and connective tissue disorders	72 (9.8%)	81 (10.3%)	67 (8.5%)	148 (9.4%)
Arthralgia	21 (2.9%)	27 (3.4%)	24 (3.0%)	51 (3.2%)
Back pain	8 (1.1%)	16 (2.0%)	15 (1.9%)	31 (2.0%)
Myalgia	6 (0.8%)	11 (1.4%)	11 (1.4%)	22 (1.4%)
General disorders and administration site conditions	39 (5.3%)	68 (8.6%)	76 (9.6%)	144 (9.1%)
Fatigue	15 (2.0%)	22 (2.8%)	22 (2.8%)	44 (2.8%)
Injection site erythema	3 (0.4%)	8 (1.0%)	13 (1.6%)	21 (1.3%)
Skin and subcutaneous tissue disorders	55 (7.5%)	69 (8.7%)	63 (8.0%)	132 (8.3%)
Pruritus	10 (1.4%)	17 (2.2%)	14 (1.8%)	31 (2.0%)
Psoriasis	16 (2.2%)	3 (0.4%)	10 (1.3%)	13 (0.8%)
Ecchymosis	2 (0.3%)	3 (0.4%)	8 (1.0%)	11 (0.7%)
Gastrointestinal disorders	48 (6.6%)	61 (7.7%)	63 (8.0%)	124 (7.8%)
Diarrhoea	12 (1.6%)	20 (2.5%)	18 (2.3%)	38 (2.4%)
Nausea	11 (1.5%)	12 (1.5%)	12 (1.5%)	24 (1.5%)

**Table 7** Number of subjects with 1 or more treatment-emergent adverse events (with frequency of 1% or greater in CNTO 1275-treated subjects) through Week 12 by MedDRA system-organ class and preferred term; treated subjects in psoriasis Phase 2 and Phase 3

	CNTO 1275			
	Placebo	45 mg	90 mg	Combined
Respiratory, thoracic and mediastinal disorders	32 (4.4%)	44 (5.6%)	47 (5.9%)	91 (5.8%)
Pharyngolaryngeal pain	7 (1.0%)	10 (1.3%)	13 (1.6%)	23 (1.5%)
Cough	11 (1.5%)	8 (1.0%)	10 (1.3%)	18 (1.1%)
Nasal congestion	3 (0.4%)	8 (1.0%)	5 (0.6%)	13 (0.8%)
Psychiatric disorders	11 (1.5%)	22 (2.8%)	18 (2.3%)	40 (2.5%)
Depression	3 (0.4%)	9 (1.1%)	5 (0.6%)	14 (0.9%)
Insomnia	5 (0.7%)	8 (1.0%)	4 (0.5%)	12 (0.8%)
Vascular disorders	14 (1.9%)	19 (2.4%)	16 (2.0%)	35 (2.2%)
Hypertension	11 (1.5%)	13 (1.6%)	8 (1.0%)	21 (1.3%)

The overall rate of AEs observed in the studies provided with the initial application was not statistically different between the groups over 12-week period. However the lack of a long-term placebo group made interpretation of any difference difficult. Overall, with the additional 6 months follow-up provided during the procedure:

The AE profiles observed were consistent with the patterns and rates of AEs reported in the initial MAA.

Duration of exposure or cumulative exposure to ustekinumab did not have an apparent impact on safety. Rates of AEs, SAEs, infections, and AEs leading to study agent discontinuation did not increase over time or with increasing length of exposure, and rates of these events did not appear to increase with increasing cumulative drug exposure.

The safety of retreatment was evaluated with additional data from the randomized withdrawal period of the PHOENIX 1 study. The overall pattern of AEs reported after retreatment with ustekinumab was generally consistent with the pattern reported in the overall subject population. Rates of SAEs remained low and no cases of anaphylaxis or serum-sickness like reactions were reported with retreatment.

Safety was also evaluated by analyzing targeted AEs that were identified based upon drug mechanism of action and specific risks in the target patient population. Rates of serious infections, malignancies, and serious cardiovascular events were low in all treatment groups. With the additional 6 months, follow-up-adjusted rates of these events remained generally comparable to rates reported in the initial MAA (see Table 29-6).

No additional adverse drug reactions (ADRs) were identified since the initial MAA.

Antibody rates remained low (approximately 5% across the Phase 2 and 3 psoriasis studies). Consistent with the initial MAA, there was no apparent relationship between development of antibodies to ustekinumab and development of injection site reactions.

Table 29-6: Comparison of numbers of infection, CVS and malignancy SAEs between the initial application and the more recent data.

**Table 29-6 Summary of event rates for serious infections, major adverse cardiovascular events, and incidence of neoplasm; treated subjects in psoriasis Phase 2 and Phase 3**

	Initial MAA Ustekinumab			120-day Safety Update Report <sup>a</sup> Ustekinumab		
	45 mg	90 mg	Combined	45 mg	90 mg	Combined
Subjects treated <sup>b</sup>	1110	1156	2266	1110	1156	2266
Total subject years of follow-up <sup>c</sup>	725	742	1467	1113	1138	2251
Event rate per hundred subject-years (number of events)						
Serious infections	0.83 (6)	1.21 (9)	1.02 (15)	1.08 (12)	1.05 (12)	1.07 (24)
Major adverse cardiovascular events <sup>d</sup>	0.69 (5)	0.54 (4)	0.61 (9)	0.54 (6)	0.35 (4)	0.44 (10)
Incidence rate per hundred subject-years (number of subjects)						
Neoplasms (malignant)	1.52 (11)	1.08 (8)	1.30 (19)	1.26 (14)	1.06 (12)	1.16 (26)
NMSC	0.83 (6)	1.08 (8)	0.96 (14)	0.63 (7)	0.97 (11)	0.80 (18)
Malignancy other than NMSC	0.69 (5)	0.00 (0)	0.34 (5)	0.63 (7)	0.09 (1)	0.36 (8)
Lymphoma	0	0	0	0	0	0

<sup>a</sup> Refer to Module 5.3.5.3, 120-day Safety Update Report.

<sup>b</sup> Placebo crossover subjects were included in ustekinumab columns after crossover to ustekinumab.

<sup>c</sup> The total subject years of follow-up for malignancy is slightly lower since only the first event is counted in the calculation of incidence per 100 subject-years.

<sup>d</sup> Major adverse cardiovascular events include cardiovascular death, MI, or stroke.

- **Serious adverse event/deaths/other significant events**

A 53-year-old woman in the 90 mg group in the PHOENIX 1 study was hospitalized for disseminated, cutaneous herpes zoster that developed 3 days after her first administration of study agent. She was treated with acyclovir, and the viral infection resolved without complications, but led to permanent discontinuation of study agent.

The 2 most frequently reported classes of SAEs were cardiac disorders and infections and infestations, both of which occurred in 0.3% of subjects in the combined ustekinumab group. SAEs in the cardiac system-organ class were reported in 0.0%, 0.1%, and 0.5% of subjects in the placebo, 45 mg, and 90 mg groups, respectively. SAEs in the infections and infestations system organ class were reported in 0.4%, 0.0%, and 0.5% of subjects in these respective groups. No consistent pattern of individual SAEs was observed in the pooled psoriasis data or in the individual studies.

Through the End of the Reporting Period: Through the end of the reporting period, the proportions of subjects who had at least 1 SAE was comparable between the 45 mg and 90 mg groups (4.1% and 3.4%, respectively) The proportions of subjects who had at least 1 SAE in the placebo → 45 mg and the placebo → 90 mg groups did not increase with increased dose (3.1% and 1.6%, respectively). Other SAEs occurred at comparable rates in subjects in the 45 mg and 90 mg groups. Of note, the proportion of serious infections through the end of the reporting period (0.7%) was comparable to the proportion of subjects who were hospitalized for a serious infection in the year prior to study enrolment.

Infections, cardiac and psychiatric disorders were slightly higher in the 90mg dose group. This may be related to the higher weight and pre-existing risk factors in these subjects. There were more malignancies in the treated group but overall standardised incidence ratios suggested no difference between placebo and treated patients.

A 33-year-old man died during the psoriasis clinical studies from sudden cardiac death thought to result from a dilated cardiomyopathy. The subject was in the 90 mg group, and his death occurred 5 days after receiving the Week 4 administration of ustekinumab. Relevant medical history included hypertension, hyperlipidemia, and seizure disorder, and the subject had a syncopal episode 9 weeks before being randomised (which was unknown to the investigator).

Histology analysis of the cardiomyopathy-related death revealed that the heart was hypertrophied (weighing 640 gm, compared to a normal weight for height and gender of 390 gm). There was no significant coronary artery disease, valvular disease, or other structural abnormalities. There was no microscopic evidence of myocarditis or ischemic injury. The findings were characteristic of dilated cardiomyopathy. There were no microscopic abnormalities other than the evidence of hypertrophy, and no evidence for an underlying etiology. It was noted that hypertrophy of the heart is a slow, progressive process that occurs over years and therefore it is almost impossible for a heart to hypertrophy to that extent during the 5 weeks that the subject was in the clinical psoriasis study. This additional data on the case of death with cardiomyopathy clarified the probable cause and made it unlikely that ustekinumab was implicated.

No deaths were reported through week 76 for PHOENIX 1. The two deaths observed in subjects participating through Week 52 in the PHOENIX 2 study were probably not linked to ustekinumab. One subject (placebo → 45 mg group) was a 63-year-old man who died from a possible aspiration (final pathology report pending) after reaching Week 44 of the study (crossover to active treatment occurred at Week 12). The other subject was a 43-year-old woman who died from a post-operative intra-abdominal bleed resulting in hemorrhagic shock the day after undergoing an elective hysterectomy and an umbilical hernia repair. She had reached Week 60 of the study and was in the 90 mg group.

- **Laboratory findings**

In the Phase 1 and Phase 2 studies, review of the T-lymphocyte subset profiles indicated a high degree of variability and no consistent effect of ustekinumab on T-lymphocyte subsets. Overall, there was no evidence of any relationship between ustekinumab and changes in lymphocyte subset counts. While markedly abnormal changes in overall lymphocytes were common in all studies (occurring in more than 1% of the study populations), rates were generally not higher in ustekinumab-treated subjects than in placebo-treated subjects, and no dose-effect was observed.

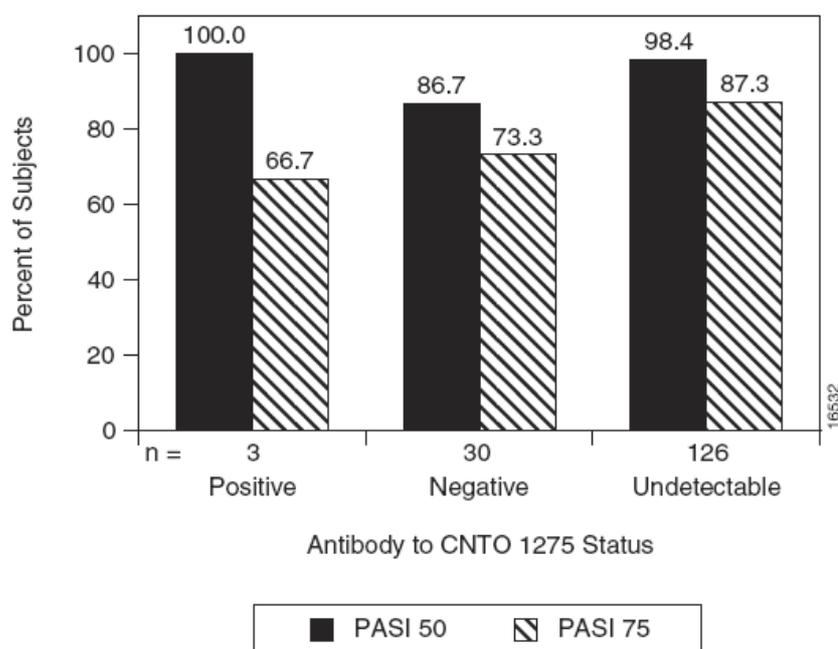
In Phase 2, markedly abnormal increases in non-fasting glucose levels were observed in more ustekinumab-treated subjects (9.5%) than subjects treated with placebo (4.5%) during the placebo-controlled period. Nonetheless, more detailed analyses were undertaken in Phase 3, including analyses of fasting glucose levels and hemoglobin A1c. Analyses in each of the Phase 3 studies suggested that ustekinumab does not adversely impact fasting glucose levels or glucose homeostasis.

No significant dose-related changes were noted in CRP or D-dimers.

- **Immunological events**

The incidence of antibodies to ustekinumab was low and was similar (approximately 4%) across the psoriasis studies. Of the 753 subjects treated with ustekinumab in PHOENIX 1, 746 had samples that were tested for antibodies to ustekinumab. Between Week 52 and Week 76, no additional subjects became antibody positive.

Most of the subjects in the withdrawal therapy groups at Week 52 had undetectable serum ustekinumab concentrations, suggesting that antibody positive rate did not increase on re-treatment. In addition, the presence of antibodies did not preclude a response to ustekinumab.



**Figure 6** Percent of subjects achieving PASI responses at Week 76 by antibody to CNTO 1275 status through Week 76; treated subjects who were randomized to q12 week dosing at Week 40

- **Safety in special populations**

No specific studies were performed in patients > 65g.

No studies were performed in children.

- **Safety related to drug-drug interactions and other interactions**

None identified, but patients on immunosuppressive therapy were excluded from the trials.

- **Discontinuation due to adverse events**

No patterns emerged from the AEs that led to discontinuation.

During the common placebo-controlled portions of the Phase 2 and 3 studies, the proportions of subjects who discontinued study agent because of an AE was comparable among the treatment groups (1.9%, 1.1%, and 1.4% in the placebo, 45 mg, and 90 mg groups, respectively). Most events occurred in only 1 subject in each treatment group, with the exception of psoriasis and exfoliative dermatitis, which occurred in 5 and 2 subjects, respectively, in the placebo group. The most frequently reported AE leading to study agent discontinuation in ustekinumab-treated subjects occurred in the system-organ class of neoplasms benign, malignant, and unspecified (0.0%, 0.3%, and 0.3% in the placebo, 45 mg, and 90 mg groups, respectively). Two subjects each in the 45 mg and 90 mg groups discontinued study agent because of neoplasms (1 subject with a basal cell cancer in each group; 1 subject with prostate cancer in the 45 mg group and 1 subject with a benign meningioma in the 90 mg group). Discontinuation of study agent was mandatory per protocol in subjects diagnosed with a malignancy of any kind, including skin cancer. Of note, 2 subjects in the placebo group also discontinued study agent because of a malignancy or a malignancy-related AE but are not listed in this system-organ class.

Through the end of the reporting period, the frequency of subjects who discontinued study agent because of an AE was low. The proportions of subjects who had at least 1 AE leading to study agent discontinuation were comparable between the 45 mg and 90 mg groups (3.0% in each group), and comparable in the placebo crossover groups (1.9% and 0.8% in the placebo → 45 mg and placebo → 90 mg groups, respectively).

Among the 124 subjects who were evaluated for safety of retreatment, 2 subjects in the 45 mg group had AEs leading to study agent discontinuation after retreatment with ustekinumab. 1 subject discontinued study agent for psoriasis, and 1 subject discontinued study agent for cellulitis, urinary tract infection, nephrolithiasis, compartment syndrome, headache, and anxiety. No clear pattern of

AEs was observed. In particular, no AEs of anaphylaxis or serum sickness-like reactions were reported.

- **Post marketing experience**

None.

- **Discussion on clinical safety**

The adverse events predominantly associated with ustekinumab are infection and cardiovascular AEs. These AEs seemed more common in the higher dose group, however the safety database initially provided was small and there was no comparator group to assess whether the AEs are treatment-related. Two pivotal trials supported by a phase 2 and two phase 1 trials were performed. 1970 patients only were exposed to ustekinumab in clinical studies. Of these 1599 (85%) were psoriasis. Overall 14% of patients were exposed for over 6 months, and none were exposed for more than one year. In the psoriasis patients only 5% were exposed for at least 6 months.

From the initial data the safety profile seemed similar to placebo over a 12-week period but there was no longer term comparator group. Further data from the then ongoing trial at week 52 were requested. There was a slight increase in infection (including one disseminated herpes infection) and there was one sudden death (cardiomyopathy-related) in a 33yr old man -and both of these occurred in patients on the high dose. The incidence of anti-ustekinumab antibody detection was limited as serum ustekinumab interfered with the assay. 5% of subjects in PHOENIX 1 were classed as antibody positive, and 47% as undetectable.

The additional safety data provided did not identify new risks. The side effects included infection (including serious infection), cardiovascular side effects, malignancies, antibody formation and psychiatric disorders. The final safety database was significant, with data on a total of 2266 treated subjects, of whom 1970 treated for at least 6 months, 1285 treated for at least 12 months and 373 treated for at least 18 months.

In the event of a significant adverse event (e.g. the development of a neoplasm) the long half-life of the product is a disadvantage. It should be noted that the pharmacodynamic effect of ustekinumab is irreversible until the plasma levels are very low and the function of the suppressed cell populations has recovered, which may be a period of months.

Risks associated with potentially life-long immunosuppression exist, in common with other immunosuppressives. Risks pertaining to infections, malignancies, hypersensitivity reactions, depression, concomitant immunosuppressive medication, pregnancy, lactation, vaccinations and comorbidities (such as marked renal or hepatic impairment) are detailed in the SPC. In addition, Stelara is contraindicated in patients with a clinically important, active infection.

## **2.5 Pharmacovigilance**

### **Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the Applicant generally fulfils the legislative requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

### **Risk Management Plan**

The MAA submitted a risk management plan, which included a risk minimisation plan.

**Table:** Overall summary of Risk Management Plan.

Safety Concern	Proposed Pharmacovigilance Activities  (Routine and Additional)	Proposed Risk Minimization Activities  (Routine and Additional)
<p><b>Potential risks</b></p> <p>Serious infections</p> <p>Malignancy</p>	<p><b>Routine PV activities:</b></p> <ul style="list-style-type: none"> <li>• AE collection and single case processing</li> <li>• Aggregate reports: Periodic Safety reporting</li> <li>• Surveillance and signal detection</li> <li>• Product information</li> </ul> <p><b>Additional PV activities:</b></p> <ul style="list-style-type: none"> <li>• SAE follow-up questionnaire selected postmarketing AE reports</li> </ul> <p><b>Additional clinical trial data:</b></p> <ul style="list-style-type: none"> <li>• Long-term extensions of Phase 3 PSO studies</li> <li>• Etanercept comparator study in PSO</li> <li>• Phase 2b study in Crohn’s disease</li> <li>• Phase 1, Phase 2/3, and Phase 3 studies in Asian region</li> </ul> <p><b>Prospective Cohort Studies/Registries:</b></p> <ul style="list-style-type: none"> <li>• PSOLAR</li> <li>• Nordic Database Initiative</li> </ul> <p><b>Potential additional data source:</b></p> <ul style="list-style-type: none"> <li>• Claims Database(s)</li> </ul>	<p><b>Routine Risk Minimization Activities:</b></p> <p>Guidance is provided in the Contraindications, Warnings/Precautions and Undesirable Effects sections of the SPC.</p> <p>Contraindication in section 4.3 “Contraindications”</p> <p>“Clinically important, active infection.”</p> <p>Warning in section 4.4 “Special warnings and precautions for use”</p> <p>“Infections”</p> <p><i>“ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA (see section 4.8).</i></p> <p><i>Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3).</i></p> <p><i>Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.</i></p> <p><i>Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves.”</i></p> <p>Warning in section 4.4 “Special warnings and precautions for use”</p> <p>“Malignancies”</p> <p><i>“Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies developed cutaneous and non cutaneous malignancies (see section 4.8).</i></p> <p><i>No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.”</i></p>

Safety Concern	Proposed Pharmacovigilance Activities  (Routine and Additional)	Proposed Risk Minimization Activities  (Routine and Additional)
		<p>Infections and infestations are listed in section 4.8 of the SPC.</p> <p><b>Additional Risk Minimization Activities:</b></p> <p>STELARA Education Program including TB screening, appropriate patient selection, key efficacy and safety information</p>
CV events	<p><b>Routine PV activities:</b></p> <ul style="list-style-type: none"> <li>• AE collection and single case processing</li> <li>• Aggregate reports: Periodic Safety reporting</li> <li>• Surveillance and signal detection</li> <li>• Product information</li> </ul> <p><b>Additional PV activities:</b></p> <ul style="list-style-type: none"> <li>• SAE follow-up questionnaire selected postmarketing AE reports</li> </ul> <p><b>Additional clinical trial data:</b></p> <ul style="list-style-type: none"> <li>• Long-Term Extensions of Phase 3 PSO studies</li> <li>• Etanercept comparator study in PSO</li> <li>• Phase 2b study in Crohn's disease</li> <li>• Phase 1, Phase 2/3, and Phase 3 studies in Asian region</li> </ul> <p><b>Prospective Cohort Studies/Registries:</b></p> <ul style="list-style-type: none"> <li>• PSOLAR</li> <li>• Nordic Database Initiative</li> </ul> <p><b>Potential additional data source:</b></p> <ul style="list-style-type: none"> <li>• Claims Database(s)</li> </ul>	None
Systemic hypersensitivity reactions	<p><b>Routine PV activities:</b></p> <ul style="list-style-type: none"> <li>• AE collection and single case processing</li> <li>• Aggregate reports: Periodic Safety reporting</li> <li>• Surveillance and signal detection</li> <li>• Product information</li> </ul> <p><b>Additional clinical trial data:</b></p> <ul style="list-style-type: none"> <li>• Long-term extensions of Phase 3 PSO studies</li> </ul>	<p><b>Routine Risk Minimization Activities:</b></p> <p>Guidance is provided in the Warnings/Precautions and Undesirable Effects sections of the SPC.</p> <p>Warning in section 4.4 "Special warnings and precautions for use"</p> <p><i>"Hypersensitivity reactions"</i></p> <p><i>"If an anaphylactic or other serious allergic reaction occurs, administration of STELARA should be discontinued immediately and appropriate therapy instituted (see section 4.8)."</i></p>

Safety Concern	Proposed Pharmacovigilance Activities  (Routine and Additional)	Proposed Risk Minimization Activities  (Routine and Additional)
	<ul style="list-style-type: none"> <li>• Etanercept comparator study in PSO</li> <li>• Phase 2b study in Crohn's disease</li> <li>• Phase 1, Phase 2/3, and Phase 3 studies in Asian region</li> </ul> <p><b>Prospective Cohort Studies/Registries:</b></p> <ul style="list-style-type: none"> <li>• PSOLAR</li> <li>• Nordic Database Initiative</li> </ul> <p><b>Potential additional data source:</b></p> <ul style="list-style-type: none"> <li>• Claims Database(s)</li> </ul>	<p>Injection site reactions are listed under "General disorders and administration site conditions" in section 4.8 of the SPC.</p>
Serious depression	<p><b>Routine PV activities:</b></p> <ul style="list-style-type: none"> <li>• AE collection and single case processing</li> <li>• Aggregate reports: Periodic Safety reporting</li> <li>• Surveillance and signal detection</li> <li>• Product information</li> </ul> <p><b>Additional clinical trial data:</b></p> <ul style="list-style-type: none"> <li>• Long-term extensions of Phase 3 PSO studies</li> <li>• Etanercept comparator study in PSO</li> <li>• Phase 2b study in Crohn's disease</li> <li>• Phase 1, Phase 2/3, and Phase 3 studies in Asian region</li> </ul> <p><b>Prospective Cohort Studies/Registries:</b></p> <ul style="list-style-type: none"> <li>• PSOLAR</li> </ul> <p><b>Potential additional data source:</b></p> <ul style="list-style-type: none"> <li>• Claims Database(s)</li> </ul>	<p><b>Routine Risk Minimization Activities:</b></p> <p>Depression is listed in section 4.8 of the SPC.</p>

Safety Concern	Proposed Pharmacovigilance Activities  (Routine and Additional)	Proposed Risk Minimization Activities  (Routine and Additional)
Exposure during pregnancy	<p><b>Routine PV activities:</b></p> <ul style="list-style-type: none"> <li>• AE collection and single case processing</li> <li>• Aggregate reports: Periodic Safety reporting</li> <li>• Surveillance and signal detection</li> <li>• Product information</li> </ul> <p><b>Additional clinical trial data:</b></p> <ul style="list-style-type: none"> <li>• Long-term extensions of Phase 3 PSO studies</li> <li>• Etanercept comparator study in PSO</li> <li>• Phase 2b study in Crohn’s disease</li> <li>• Phase 1, Phase 2/3, and Phase 3 studies in Asian region</li> </ul> <p><b>Prospective Cohort Studies/Registries:</b></p> <ul style="list-style-type: none"> <li>• PSOLAR</li> <li>• Pregnancy Research Initiative</li> </ul> <p><b>Potential additional data source:</b></p> <ul style="list-style-type: none"> <li>• Claims Database(s)</li> </ul>	<p><b>Routine Risk Minimization Activities:</b></p> <p>Guidance is provided in the Pregnancy and Lactation section of the SPC.</p> <p>Section 4.6 “Pregnancy and Lactation”</p> <p><i>“Pregnancy”</i>  <i>“There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy. Women of childbearing potential should use effective methods of contraception during treatment and up to 15 weeks after treatment.”</i></p> <p><i>“Lactation”</i>  <i>“It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown excretion of ustekinumab at low levels in breast milk. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.”</i></p>
<b>Important missing information</b>		
<ul style="list-style-type: none"> <li>• Use in pediatrics</li> <li>• Use in patients with hepatic impairment</li> <li>• Use in patients with renal impairment</li> <li>• Use in patients with latent TB or prior history of TB</li> <li>• Use in patients with concurrent malignancy or a history of malignancy</li> <li>• Use after recent vaccination with live bacterial or live viral</li> </ul>	<p><b>Routine PV activities:</b></p> <ul style="list-style-type: none"> <li>• AE collection and single case processing</li> <li>• Aggregate reports: Periodic Safety reporting</li> <li>• Surveillance and signal detection</li> <li>• Product information</li> </ul> <p><b>Additional clinical trial data:</b></p> <ul style="list-style-type: none"> <li>• Long-term extensions of Phase 3 PSO studies</li> <li>• Etanercept comparator study in PSO</li> <li>• Phase 2b study in Crohn’s disease</li> <li>• Phase 1, Phase 2/3, and Phase 3 studies in Asian region</li> </ul> <p><b>Prospective Cohort Studies/Registries:</b></p> <ul style="list-style-type: none"> <li>• PSOLAR</li> </ul>	<p><b>Routine Risk Minimization Activities:</b></p> <p>Guidance is provided in the Warnings/Precautions of the SPC.</p> <p>Warning in section 4.4 “Special warnings and precautions for use”</p> <p><i>“Children and adolescents (&lt; 18 years)”</i>  <i>“STELARA is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.”</i></p> <p><i>“Hepatic and renal impairment”</i>  <i>“Specific studies have not been conducted in patients with hepatic and renal impairment (see section 4.2).”</i></p> <p><i>“Infections”</i>  <i>“Treatment of latent tuberculosis infection should</i></p>

Safety Concern	Proposed Pharmacovigilance Activities  (Routine and Additional)	Proposed Risk Minimization Activities  (Routine and Additional)
<ul style="list-style-type: none"> <li>• Use in patient with active infections including HIV, hepatitis B, or hepatitis C</li> <li>• Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy</li> <li>• Use in patients with other forms of PSO</li> <li>• Use in patients of different ethnic origins</li> </ul>	<ul style="list-style-type: none"> <li>• Nordic Database Initiative</li> </ul> <p><b>Potential additional data source:</b></p> <ul style="list-style-type: none"> <li>• Claims Database(s)</li> </ul>	<p><i>be initiated prior to administering STELARA. Anti tuberculosis therapy should also be considered prior to initiation of STELARA in patients <u>with a history of latent or active tuberculosis</u> in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.”</i></p> <p><i>“Malignancies”</i>  <i>“No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.”</i></p> <p><i>“Vaccinations”</i>  <i>“It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.</i></p> <p><i>Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations”</i></p> <p><i>“Concomitant immunosuppressive therapy”</i>  <i>The safety and efficacy of STELARA in combination with other immunosuppressants, including biologics, or phototherapy have not been evaluated. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).</i></p>

The CHMP, having considered the data submitted in the MA application is of the opinion that some risk minimisation activities are necessary for the safe and effective use of the medicinal product.

Within the RMP, there are considered to be no identified risks. Potential Risks identified are serious infections, malignancy, CV events, serious systemic hypersensitivity reactions and exposure during pregnancy. Immunogenicity is to be considered a potential risk and the Applicant has been requested to include pharmacological class effects of recombinant humanised monoclonal antibodies as potential risks.

In addition to routine pharmacovigilance the company has proposed to carry out additional studies.

- Long-term extensions of the two Phase 3 PSO studies are ongoing, with plans to follow patients up for 5 years from the initial administration.
- An etanercept comparator study is ongoing.
- A PSO registry in the US is currently ongoing and collecting data on up to 4000 patients using ustekinumab.
- A Nordic database initiative is planned, to collect data on adverse events and pregnancies in patients exposed to ustekinumab.
- Follow up questionnaires will collect information on patients reporting certain AEs.
- A Pregnancy Research Initiative is ongoing. This is a prospective 5 year observational study of pregnancy outcomes in pregnant women with prenatal exposure to ustekinumab.
- A paediatric program is being developed.

Proposals should be submitted to collect data in patients of other ethnic origins. Detailed plans should be set out on how the risk of TB in all adults will be investigated.

Educational programmes are proposed to minimise the risk of serious infections and the risk of malignancies. The educational materials should be submitted.

#### *Pharmacovigilance Plan*

This is satisfactory and will involve collection of data from patients at registries in the USA and also plans to collect data from patients in Europe.

## **2.6 Overall conclusions, risk/benefit assessment and recommendation**

### **Quality**

Based on the submitted data, the marketing authorisation application for Stelara is recommended for approval based on quality grounds.

### **Non-clinical pharmacology and toxicology**

The non-clinical data provided showed that Stelara is generally well tolerated under a regimen of twice weekly subcutaneous dosing at 45 mg/kg for 6 months in cynomolgus monkeys. Adequate margins of exposure over the human clinical exposure were demonstrated. No target organs were identified and there was no delayed toxicity after dosing had stopped. The possibility of immune suppression could not be ruled out in the case of one animal in the 6-month study that developed bacterial enteritis.

In the 6-month repeat-dose study and the embryo-fetal developmental toxicity study, antibodies to ustekinumab were found in control samples, and these events were noted clearly explained.

Overall, it was not possible to discern whether there had been an anti-antibody response to ustekinumab, although some animals were noted to have greater clearance than others. This was not considered to have invalidated the studies and the pharmacokinetic indices were considered to show that adequate exposure was demonstrated.

ustekinumab had no effects on male fertility as assessed by spermatogenic measurements only. In females, there were no effects on gestation, parturition, lactation or morphology and development of the offspring.

## **Efficacy**

The efficacy of Stelara in PASI, PGA and DLQI scores was statistically significantly superior to placebo and etanercept in plaque psoriasis after 12 weeks of treatment. The proportion of patients achieving PASI 75 response at week 12 was respectively 72.2% and 65% on 45 mg and 90mg respectively, versus 56.8% on Etanercept. Approximately 35 to 50% of subjects achieved a PASI 90 response at Week 12. Similar efficacy with CNTO 1275 (STELARA, ustekinumab) treatment was observed when efficacy was assessed using the PGA.

Retreatment was effective and a response was maintained with continued treatment. The availability of an injection which can be self-administered and which is required only once every 12 weeks would benefit patients with severe disease who need immunosuppressive therapy. The lack of identified cumulative toxicity with biological therapies to date (in contrast to PUVA, methotrexate etc.) offers additional benefits. Additional data from the ACCEPT trial demonstrated superiority compared with etanercept at 12 weeks.

## **Safety**

In common with other immunosuppressives, the risks associated with potentially life-long immunosuppression exist. In order to assess the degree of impairment of the systemic immune system the Applicant has committed to provide a protocol for a study investigating vaccine responses within an agreed pre-defined timeframe.

The risks identified with the additional safety data provided during the procedure are similar to those identified from the data submitted initially. The side effects include infection (including serious infection), cardiovascular side effects, malignancies, antibody formation and psychiatric disorders. These risks have been highlighted in the SPC, with the exception of cardiovascular disease, which is listed as potential risk in the RMP. Follow-up information about this potential risk will be made available post-marketing by means of regular PSURs.

The complete safety database is significant and consists of data on 2266 total treated subjects (1970 treated for at least 6 months, 1285 treated for at least 12 months and 373 treated for at least 18 months).

Risks pertaining to infections, malignancies, hypersensitivity reactions, depression, concomitant immunosuppressive medication, pregnancy, lactation, vaccinations and co-morbidities (such as marked renal or hepatic impairment) are detailed in the SPC. In addition, Stelara is contraindicated in patients with a clinically important, active infection.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- **User consultation**

A user testing of the PL for Stelara was performed. Following an audience design step and a pilot test, two rounds of user testing (n=10) were performed on participants from the general public. Although the expert patient had psoriasis, the subjects who participated in the user trial did not have psoriasis as an inclusion or exclusion criterion. This was considered satisfactory. The conclusions were clear, concise and well organised and the criteria of 90% finding and 90% understanding was reached in all questions.

### **Risk-benefit assessment**

The efficacy of ustekinumab was demonstrated, together with long-term efficacy and also efficacy and safety of re-treatment. Superiority compared with etanercept was demonstrated. The subcutaneous route of administration offers advantages over intravenous administration in terms of comfort and because it offers the possibility of home therapy. Infrequent injections are also a benefit.

The Applicant provided during the procedure significantly more safety data and in addition presented a trial where an active comparator was used (etanercept). With the additional data provided by the Applicant during the procedure no new safety signals were detected and the larger safety database did not give rise to new concerns.

Because of the nature of action of Stelara (blocking two cytokines) and the unexpected increased incidence of cardiovascular and psychiatric disease (which may be related to the treatment) the indicated group has been restricted to “those who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA”. The overall benefit/risk ratio of Stelara in this restricted indication is positive.

The identified risks of infection, malignancy, psychiatric and immunological AEs are highlighted in the SPC and addressed in the RMP, and the quality FUM and vaccine response post-marketing studies commitment are fulfilled.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. The following additional risk minimisation activities were required: see as details in section 2.3.

### **Recommendation**

Based on the review of the data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Stelara (ustekinumab) in the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA, was favourable and therefore recommended the granting of the marketing authorisation.