EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/CHMP/129351/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stelara

International non-proprietary name: ustekinumab

Procedure no. EMEA/H/C/000958/II/0037

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR	American College of Rheumatology
AE	adverse event
ADR	adverse drug reaction
ASA	aminosalicylate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	Clinical Study Report
CV	cardiovascular
DLQI	Dermatology Life Quality Index
DMARD	disease-modifying anti-rheumatic drug
EMA	European Medicines Agency
EU	European Union
IL	interleukin
ISS	integrated summary of safety
IV	intravenous
LIV	liquid in vial
LTE	long-term extension
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MAH	Marketing Authorization Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
MS	multiple sclerosis
MTX	Methotrexate
NMSC	nonmelanoma skin cancer
NSAID	non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PsA	psoriatic arthritis
PSOLAR	Psoriasis Longitudinal Assessment and Registry
PSUR	postmarketing surveillance update report
PUVA	psolaren plus ultraviolet A
q8w	every 8 weeks
q12w	every 12 weeks
SAE	serious adverse event
SPC/SmPC	Summary of Product Characteristics
TNFα	tumor necrosis factor alpha
TRANSIT	An exploratory TRial to Assess Naturalistic Safety and efficacy outcomes In patients Transitioned to ustekinumab from previous methotrexate therapy
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 variation of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 7 October 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Stelara	USTEKINUMAB	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1). Section 1 of the Package Leaflet has been updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/292/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/226/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Greg Markey** **Co-Rapporteur:** **David Lyons**

Submission date:	7 October 2013
Start of procedure:	25 October 2013
Rapporteur's preliminary assessment report circulated on:	19 December 2013
Co-Rapporteur's preliminary assessment report circulated on:	16 December 2013
PRAC RMP advice and assessment overview adopted by PRAC:	9 January 2014
Rapporteur's and Co-Rapporteur's joint assessment report circulated on:	14 January 2014
CHMP opinion:	23 January 2014

2. Scientific discussion

2.1. Introduction

STELARA (ustekinumab) is classified as an interleukin receptor inhibitor with ATC subgroup code L04AC. Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells.

STELARA is currently approved in the following indications:

Plaque psoriasis

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) and PUVA (psoralen and ultraviolet A).

Psoriatic arthritis (PsA)

STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

The purpose of this submission is to support an update to the Stelara EU-SmPC to change the psoriasis indication to the following (additions in **bold and underlined**, deletions in ~~strikethrough~~):

Plaque psoriasis

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) ~~and~~**or** PUVA (psoralen and ultraviolet A).

A new version (version 11.0) of the Stelara EU Risk management plan (RMP) has been included in this submission.

STELARA was approved in the European Union (EU) on 16 January 2009 for the treatment of adult patients with moderate to severe chronic plaque psoriasis. Since the first approval of STELARA in Canada (12 December 2008), STELARA has been approved globally in over 75 countries for the treatment of moderate to severe plaque psoriasis. On 25 July 2013, STELARA received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the treatment of active psoriatic arthritis (PsA).

At the time of the initial STELARA marketing authorization application (MAA), the marketing authorization holder (MAH) proposed the following psoriasis indication wording, in line with the studied population and with the approved indication wording of the anti-tumour necrosis factor alpha (TNFα) agents:

"STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate or PUVA."

Based on the review for the initial MAA, STELARA was deemed approvable but with a restricted indication; the indicated population was restricted to those who had failed at least 3 systemic therapies. The rationale for this restriction was that ustekinumab was a new agent with a novel mechanism of action planned to be used in a non-life threatening condition for extended periods of time. A longer clinical experience would be required before a broader indication could be granted. In view of this, the CHMP recommended limiting the indicated group to those who have failed at least 3 major therapies. The anti-TNFα agents have broader long-term safety data (including in conditions other than psoriasis) than ustekinumab and have a well-known safety profile. The limited indication would be expected to be changed based on satisfactory PhV and PSURs.

As a result, the MAH and the CHMP agreed to a more restrictive indication statement, which is currently in the approved SmPC.

Since the initial approval of STELARA in the EU, the MAH has submitted the following data as it became available:

- Longer-term safety data through 4 and 5 years of exposure from the C0743T08 and C0743T09 studies. These data showed that the safety profile of STELARA remained favourable and was consistent with the data submitted in the MAA. These data were reviewed by the CHMP and led to updates in the SmPC.

- Data from a large company sponsored registry (Psoriasis Longitudinal Assessment and Registry [PSOLAR]).

- Global post-marketing experience. The MAH has a robust pharmacovigilance program in place and with post-marketing data available through 30 June 2013, has completed 9 PSURs.

- Data from clinical studies in other indications including PsA and Crohn's disease.

Collectively, with these data, the MAH considers to have addressed the CHMP's statement that "The limited indication would be expected to be changed based on satisfactory PhV and PSURs." Therefore, the current application is being submitted to apply for the removal of the restriction to the STELARA psoriasis indication and to bring it in line with the indication wording of other currently approved biologics by replacing 'and' by 'or' as follows:

“STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate ~~and~~**or** PUVA.”

2.2. Clinical aspects

2.2.1. Introduction

The MAH has not conducted any new clinical trials in support of this application. The efficacy of Stelara is already known. Stelara is a highly effective treatment for adult patients with moderate to severe plaque psoriasis. The benefit of maintenance dosing is sustained over a 5-year period studied. Based on both clinical measurements of skin disease and improvement of health related quality of life, STELARA has been shown to have a positive impact on patients' lives.

The new indication claimed by the MAH is based on new safety data in conjunction with the most recent annual interval PSOLAR report.

The Phase 2 and 3 STELARA clinical studies in psoriasis, PsA, Crohn’s disease, and multiple sclerosis (MS) are briefly outlined below.

Psoriasis Clinical Studies

The global psoriasis clinical development program included 4 key studies:

- A single Phase 2 study (C0379T04).
- Three Phase 3 studies (2 placebo-controlled [C0743T08 and C0743T09] and 1 active comparator-controlled [C0743T12]).

The initial MAA was based on safety, efficacy, and clinical pharmacology data up to 18 months from the C0743T08 and up to 12 months in C0743T09. Additionally, 12 week data from the C0743T12 study comparing the efficacy and safety of STELARA with that of etanercept was submitted as supportive data in response to questions during the initial MAA procedure. Since the initial MAA, long-term safety, efficacy, and clinical pharmacology data for STELARA with up to 5 years of continuous therapy were provided from the C0743T08 and C0743T09 studies (EMA/H/C/000958/II/0028). Additionally, 24-week data from the C0743T12 study were submitted and approved for inclusion in the SmPC (EMEA/H/C/000958/II/0001). Pooled data from the 4 global psoriasis studies including up to 5 years of data from C0743T08 and C0743T09 served as the primary datasets to evaluate the safety of STELARA in psoriasis. These studies allowed inclusion of moderate to severe plaque psoriasis subjects that were candidates for systemic therapy (including phototherapy) which resulted in an enrolled population of which approximately 14% of subjects had inadequate response to, were intolerant to, or had a contraindication to at least 3 conventional systemic therapies (i.e., in line with the currently approved EU indication); hence, over 80% of the studied population failed less than 3 of these therapies.

A variation including clinical safety and efficacy data of psoriasis patients with up to 5 years of exposure to STELARA was approved by the European Medicines Agency (EMA) (EMA/H/C/000958/II/0028) on 17 January 2013 and by the EC on 19 September 2013.

Additionally, since the initial MAA, STELARA has been studied in Japanese subjects (JSN-JPN-02), Chinese subjects (C0743T23), and Taiwanese and Korean subjects (C0743T25). Furthermore, the TRANSIT study compared safety and efficacy of STELARA in psoriasis patients with inadequate response to MTX, following immediate or gradual withdrawal from MTX.

Clinical Studies in Other Indications

In addition to data from clinical studies in subjects with psoriasis, broader data are available from completed clinical studies in subjects with PsA, Crohn's disease, and MS and are described below.

Psoriatic Arthritis

The clinical development program of STELARA for PsA consisted of one placebo-controlled Phase 2 (C0743T10) and two placebo-controlled Phase 3 (CNTO1275PSA3001 and CNTO1275PSA3002) clinical studies in 1,073 subjects with active PsA despite previous or current disease-modifying anti-rheumatic drug (DMARD) and/or non-steroidal anti-inflammatory drug (NSAID) use. The Phase 2 C0743T10 study was included in the initial MAA. Since then, the 24-week signs and symptoms efficacy and safety data from the CNTO1275PSA3001 and CNTO1275PSA3002 clinical studies became available and supported an application for the treatment of PsA patients with STELARA. This variation (EMEA/H/C/000958/II/0029) received a positive CHMP opinion on 25 July 2013.

Crohn's Disease

The initial MAA included data from the Phase 2a C0379T07 study in subjects with moderately to severely active Crohn's disease. The primary study population (Population 1) consisted of subjects with Crohn's disease despite treatment with 5-aminosalicylate (5-ASA) compounds, antibiotics, corticosteroids, and/or immunomodulators. The secondary study population (Population 2) consisted of those subjects who failed to respond to the maximum approved dose and treatment regimen of infliximab for Crohn's disease as defined in the REMICADE US package insert. This study evaluated the safety of ustkekinumab intravenous (IV) 4.5 mg/kg and subcutaneous (SC) ustekinumab 90 mg. Since the MAA, data from the C0743T26 study in subjects with moderately to severely active Crohn's disease became available. C0743T26 was a Phase 2b study in 526 subjects with moderately to severely active Crohn's disease who were previously treated with anti-TNFα agent therapy. This study evaluated the safety of single IV STELARA doses up to 6 mg/kg and maintenance dosing of 90 mg SC every 8 weeks (q8w). These data have been submitted to the CHMP.

Multiple Sclerosis

The initial MAA included data from the C0743T06 study in subjects with relapsing-remitting MS. C0743T06 was a Phase 2, multicenter, double-blind, placebo-controlled, randomized study in 249 subjects. This study evaluated 4 dose regimens (maximum dose of 180 mg Weeks 0, 1, 2, 3 and then monthly through Week 19) versus placebo. The maximum dose in this study provided exposure that was significantly higher than in the psoriasis population. The program was discontinued because of lack of efficacy.

PSOLAR

The Psoriasis Longitudinal Assessment and Registry (PSOLAR, Study C0168Z03) is a multicenter, prospective, observational study that tracks the long-term safety experience and clinical status of patients with psoriasis, who are eligible to receive (or are actively receiving) systemic therapies for psoriasis. PSOLAR is part of multiple distinct post-marketing commitments to collect information on sponsor biologics indicated for plaque psoriasis, including STELARA and infliximab. The post-marketing commitment for PSOLAR was to enrol 12,000 patients with moderate to severe psoriasis, including 4,000 receiving STELARA, with the rest receiving or eligible to receive other systemic therapies, including other Sponsor and non- Sponsor biologics. Patients are to be followed for 8 years. PSOLAR was still enrolling at the time of the 23 August 2012 data cut, but since then enrolment has completed. As of 23 August 2012, 11,900 patients have enrolled in PSOLAR, with a median registry follow up of

1.83 years, and accumulated 22,918 patient years of follow up. As the PSOLAR dataset is maturing, it is already yielding meaningful safety information.

PSOLAR is a disease state registry designed to capture, summarise and compare data across different systemic therapies, biologic and non-biologic, available for treatment of moderate to severe psoriasis. As in all observational registries, physicians prescribe treatments based on usual clinical practice and standards of care. There are no treatment allocations or restrictions on the use of commercially available medications for patients. However, since participation in PSOLAR is voluntary, derived data are subject to patient selection bias, channelling bias, reporting bias, recall bias, and other confounding factors associated with a non-randomized observational study design. In an effort to address potential confounding by disease severity, only patients treated with, or eligible for, systemic therapy are recruited into the registry. In addition, recruitment of patients treated with other biologic therapies allows for comparison to a population with a similar indication for treatment. Cox proportional hazards regression methodology is being used to identify some of those variables that might be associated with select adverse outcomes of interest and to adjust for potential confounding.

Safety data collected and analysed in PSOLAR are reported to the regulatory authorities annually (last submission 30 January 2013). In the annual report analysis, patient cohorts were defined based on cumulative biologic exposure, including exposure prior to registry participation. In order to maximize the likelihood of capturing potential safety signals for STELARA, patients who were ever exposed to STELARA were included in the STELARA cohort. Patients who were never exposed to STELARA but were exposed to other sponsor biologics (infliximab or golimumab) were included in the Other Sponsor Biologic cohort. Patients who were never exposed to STELARA, infliximab, or golimumab, but were exposed to other biologics were included in the Other Non-sponsor Biologic cohort. Adverse events (AEs) and events of special interest were summarised for these biologic exposure cohorts and for a cohort of patients never exposed to any biologic.

The incident user cohort analysis (described below) complements the overall PSOLAR analysis and provides supplemental data to further support the safety findings from the annual report. Incident user cohorts were identified among STELARA patients and patients exposed to other biologics in the current analysis for this report. The incident cohort analyses were conducted to adjust for variable timing and different lengths of exposure to therapy, and to eliminate potential confounding issues for attributing safety events in the context of multiple exposures. The STELARA Incident User cohort (N=1454) represents patients who initiated STELARA as the first new biologic after enrolment in PSOLAR. The Other Sponsor Biologic Incident User cohort (N=255) is defined as the cohort of patients who initiated infliximab or golimumab as the first new biologic during registry participation. The Non-sponsor Biologic Incident user cohort (N=737) consists of patients who initiated a non-sponsor biologic as the first new biologic (primarily adalimumab, etanercept, but also alefacept, efalizumab, or other biologics) after enrolment. The AEs captured during the incident biologic exposure period were summarised for each of these cohorts.

This variation also includes available analyses on the STELARA safety profile and its comparability to anti-TNFα agents, as well as a presentation of the number of patients and duration of treatment captured in the PSOLAR registry, an analyses of melanoma and non-melanoma skin cancer (NMSC) and its relation to pre-treatment with conventional systemic therapies and in particular PUVA, in support of the MAH's position that patients should not be required to be heavily pretreated before using STELARA.

2.3. Clinical safety

2.3.1. Introduction

Since the initial MAA, substantial additional information has accrued from clinical studies, registries, and post-marketing experience that substantiates the overall safety of STELARA and its overall benefit-risk profile.

Table 1 summarises safety data in the initial MAA as well as broader and longer-term currently available safety data from the STELARA clinical study program, data from the PSOLAR registry, and comprehensive safety surveillance of the global marketing experience.

Table 1: Overview of available STELARA safety data

Data Source	Data available at the time of initial marketing authorization	Data currently available
Psoriasis Global Clinical Study Safety Data	Psoriasis Phase 2/3 clinical studies • 2,266 STELARA-treated patients with 2,251 cumulative subject-years follow-up ➢ 1,970 for ≥6 months ➢ 1,285 for ≥12 months ➢ 373 for ≥18 months	Psoriasis Phase 2/3 clinical studies • 3,117 STELARA-treated patients with 8,998 cumulative subject-years follow-up ➢ 2,414 for ≥6 months ➢ 1,855 for ≥12 months ➢ 1,697 for ≥18 months ➢ 1,482 for ≥4 years ➢ 838 for ≥5 years
Other Psoriasis Clinical Study Data	None	• Japan Phase 2b/3 (n=154) • Korea/Taiwan Phase 3 (n=116) • China Phase 3 (n=318) • TRANSIT Phase 3b/4 (n=489)
Other Clinical Study Data	Crohn's Disease • Phase 2a (n=120) Multiple Sclerosis • Phase 2 (n=200) Psoriatic Arthritis • Phase 2 (n=133)	Crohn's Disease • Phase 2a (n=120) • Phase 2b (n= 479) Multiple Sclerosis • Phase 2 (n=200) Psoriatic Arthritis • Phase 2 (n=133) • Phase 3 (n=543) • Phase 3 (n=238)
Registry Data	None	PSOLAR: • 11,900 patients overall with 22,918 cumulative patient-years follow-up ○ 3,796 STELARA-treated patients with 5,332 cumulative patient-years follow-up ➢ Median duration of follow-up = 1.83 years ➢ 2,393 patients for ≥1year ➢ 1,267 patients for ≥2 years ➢ 457 patients for ≥3 years ➢ 105 patients for ≥4 years
Postmarketing Exposure	None	200,315 estimated person-years through 30 June 2013

Clinical trial data

Analysis of Adverse Drug Reactions

The MAH evaluates safety data on an ongoing basis. The MAH's pharmacovigilance program systematically collects information on AEs from multiple sources, including clinical study data, registries, observational data, post-marketing reports, and literature, and conducts real time and

periodic medical assessments of single and aggregate cases to identify potential safety signals. Clinical study data are regularly reviewed by a multidisciplinary safety team. All AEs are reviewed on a real-time basis by the medical monitors and, in aggregate, by the safety team when the database is locked or unblinded.

Clinical Study Data

A favourable safety profile of STELARA for the treatment of moderate to severe psoriasis was demonstrated in the initial MAA. The initial MAA for STELARA included available safety data from psoriasis studies C0379T04, C0743T08, and C0743T09; these data did not reveal safety concerns with increasing duration of exposure or cumulative exposure up to approximately 18 months of treatment. The safety profile in the subpopulation of subjects who had an inadequate response to, were intolerant to, or had a contraindication to ≥1, ≥2, or ≥3 conventional systemic therapies was consistent with that observed in the overall population. Available safety data from the Phase 3 psoriasis C0743T12 comparator-controlled study, the Phase 2 MS study C0743T06, the Phase 2 PsA study C0743T10, and the Phase 2 Crohn's disease study C0379T07 were also submitted with the initial MAA.

Since the initial MAA approval, the following data has been submitted to the CHMP:

- safety data from the Phase 3 C0743T08 and C0743T09 LTE studies, the Phase 3b/4 CNTO1275PSO4004 (TRANSIT) study, and the Phase 2/3 Asia Pacific studies (C0743T23, C0743T25, and JSN-JPN-02) in psoriasis;
    - The data has been submitted with or was referenced in Stelara II-28 which was submitted on 30 August 2012 and received positive CHMP opinion on 17 January 2013.
    - The final CSR for C0743T08 was submitted as FUM 26 on 22 December 2011 and concluded on 15 March 2012.
    - The final CSR for C0743T09 was submitted as part of Stelara II-28 (see above).
    - The synopsis of the Phase 3b/4 CNTO1275PSO4004 (TRANSIT) study was submitted as part of Stelara II-28 (see above).
    - The final CSR for C0743T23 was submitted as FUM 33 on 27 February 2012 and concluded on 24 May 2012.
    - The final CSR for C0743T25 was submitted as FUM 28 on 01 November 2010 and concluded on 20 January 2011.
    - The final CSR for JSN-JPN-02 was submitted as FUM 32 on 31 January 2011 and concluded on 14 April 2011.
- the Phase 2 C0743T26 study in Crohn's disease (final CSR for C0743T26 was submitted as FUM 30 on 28 October 2011 and concluded on 19 January 2012);
- and the Phase 3 CNTO1275PSA3001 and CNTO1275PSA3002 studies in PsA. (included in variation II-29, submitted on 4 December 2012, which received a positive CHMP opinion on 25 July 2013, and variation II-36, submitted on 06 August 2013)

A summary of STELARA exposure (subject years of follow-up) and event rates for selected AEs through 1.5 years of exposure (provided in the initial MAA) and through 5 years of exposure (provided in the 5-year update) is presented in Table 2.

Table 2: Summary of event rates for selected safety events; treated subjects in global psoriasis studies

Reporting Period (Follow-up)[a]	Data in Initial MAA Up to 1.5 Years of Follow-up[a] Ustekinumab			Data in 5-Year Update Up to 5 Years of Follow-up[a] Ustekinumab		
	45 mg	90 mg	Combined	45 mg	90 mg	Combined
Subjects treated[b]	1110	1156	2266	1319	2001	3117
Total subject years of follow-up[c]	1113	1138	2251	3766	5232	8998
Event rate per hundred subject-years (number of events)						
Death	0.09 (1)	0.09 (1)	0.09 (2)	0.13 (5)	0.29 (15)	0.22 (20)
Serious infections	1.08 (12)	1.05 (12)	1.07 (24)	0.98 (37)	1.19 (62)	1.10 (99)
Major adverse cardiovascular events[d]	0.54 (6)	0.35 (4)	0.44 (10)	0.56 (21)	0.36 (19)	0.44 (40)
Incidence rate per hundred subject-years (number of subjects)						
Neoplasms (malignant)	1.26 (14)	1.06 (12)	1.16 (26)	1.23 (46)	1.06 (55)	1.13 (101)
NMSC	0.63 (7)	0.97 (11)	0.80 (18)	0.64 (24)	0.44 (23)	0.52 (47)
Malignancy other than NMSC	0.63 (7)	0.09 (1)	0.36 (8)	0.59 (22)	0.61 (32)	0.60 (54)
Lymphoma	0	0	0	0.00 (0)	0.02 (2)	0.01(2)

[a] Global psoriasis studies included in each reporting period: Up to 1.5 years follow-up: Phase 2 C0379T04 and Phase 3 (C0743T08 [Week 76] and C0743T09 [Week 52]); Up to 5 years follow-up: Phase 2 C0379T04 and Phase 3 (C0743T08 [Week 264], C0743T09 [Week 264], and C0743T12)

[b] Placebo crossover subjects were included in ustekinumab columns after crossover to ustekinumab. Placebo crossover subjects and etanercept crossover subjects were included in the ustekinumab columns after crossover to ustekinumab

[c] 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.

[d] Adjudicated major adverse CV events include adjudicated CV death, MI, or stroke.

CV = cardiovascular, MI = myocardial infarction, NMSC = nonmelanoma skin cancer, MAA = Marketing Authorization Application

Extracted from: Mod5.3.5.3/LIV 120-day Safety Update and Mod2.7.4/5YR SCS

Psoriasis Clinical Studies

Evaluation of the pooled data from the global psoriasis studies (C0379T04, C0743T08, C0743T09, and C0743T12) with up to 5 years of exposure provided the following safety information:

- A total of 3,117 subjects have been exposed to STELARA in the global psoriasis studies:
    - 1,482 were exposed for at least 4 years.
    - 838 were exposed for at least 5 years.
- These data provide a total of 8,998 subject-years of follow-up on STELARA.
- The profile of common AEs observed with additional follow-up in the pooled C0743T08 and C0743T09 studies was generally consistent with the AE profile reported at the time of the initial review and approval.
- Rates of serious adverse events (SAEs), infections, and AEs leading to study agent discontinuation remained generally comparable between 45 mg and 90 mg and stable over time, and did not reveal evidence of risks associated with increasing duration of exposure.
- The overall incidence of death was 0.22 per 100 subject-years of follow-up (95% confidence interval [CI]: 0.14, 0.34), with rates of 0.13 and 0.29 in the 45 mg and 90 mg groups, respectively. The rates of death were also lower than or consistent with what would be expected from the general US population. Based on medical review, the causes of death were considered to be cardiovascular (CV) (n=5), malignancy-related (n=5), and infection-related (n=3), and related to other causes (n=7). The greatest disparity in event rates between the 45 mg and 90 mg groups occurred in deaths considered to be related to other causes: 6 of 15 deaths in the 90 mg group were considered related to other causes (e.g., motor vehicle

accident, suicide, perforated bowel from a fall). In contrast, only 1 of 5 deaths in the 45 mg group was considered related to other causes (gunshot wound).

- Follow-up-adjusted rates of serious infections, malignancies (NMSC and malignancies other than NMSC), and MACE did not appear to increase over time. External databases were used to further evaluate rates of serious infections, malignancies other than NMSC, and myocardial infarction and stroke. Based on rates derived from external databases, the rates of these events were lower than or consistent with what would be expected from the general US population and/or psoriasis populations. These observations suggest that rates of these targeted AEs remain stable over time, and do not reveal evidence of risks associated with increasing duration of exposure.

  As expected based on published literature, a separate analysis showed that a significantly higher proportion of subjects with prior PUVA exposure reported NMSC compared with subjects with no prior PUVA exposure (2.9% [25/855] vs. 1.0% [22/2262]; $p<0.001$). Prior exposure to other treatments (ultraviolet B, conventional systemics, and biologics) demonstrated no impact on the occurrence of NMSC.

- No cases of active tuberculosis, non-tuberculous mycobacterial diseases, systemic fungal infections, or disseminated salmonellosis were reported in the global psoriasis studies with up to 5 years of exposure.

- Overall, the AE profile in subjects treated with STELARA does not suggest a role in exacerbating psoriasis.

- Through Year 5, STELARA injections were generally well-tolerated; injection-site reactions tended to be mild and self-limited, and did not lead to treatment discontinuation. Moreover, the proportion of injections associated with injection-site reactions remained low with up to 5 years of treatment and did not appear to increase over time. Overall, no association was observed between the development of antibodies to STELARA and the development of injection-site reactions.

- No subjects with serious hypersensitivity reactions associated with STELARA were identified.

- In the C0743T12 study, STELARA was compared directly to etanercept through Week 12. Over this period, STELARA therapy was well-tolerated with a safety profile generally comparable to that of etanercept.

- The rates of targeted events (malignancy [NMSC and malignancy other than NMSC], serious infection, and MACE) observed with up to 5 years of STELARA exposure were comparable to rates observed in the clinical development programs of other approved biologics including the anti-TNFα agents etanercept and adalimumab.

    - For NMSC, the overall rate of 0.52 per 100 subject years of follow-up (95% CI: 0.39, 0.70) in the ustekinumab program was comparable with or lower than the rate observed in recent safety updates from LTEs from adalimumab (0.70 per 100 subject years of follow-up) and etanercept (1.05 per 100 subject years of follow-up).

    - For malignancies other than NMSC, the overall rate of 0.60 per 100 subject years of follow-up (95% CI: 0.45, 0.78) in the ustekinumab program was comparable with the rate observed in recent safety updates from LTEs from both adalimumab (0.72 per 100 subject years of follow-up and etanercept (0.57 per 100 subject years of follow up. In addition, based on comparisons with the SEER database; the SIRs were 0.96 (95% CI:

0.65, 1.36) for adalimumab and 1.36 (95% CI: 0.90, 1.97) for etanercept, compared with 0.98 (95% CI: 0.74, 1.29) for ustekinumab.

- Rates of serious infections in STELARA-treated subjects in the global psoriasis studies were generally comparable with the incidence reported in subjects treated with other biologics approved for the treatment of psoriasis (adalimumab and etanercept).
- Updated analyses from LTEs of other biologic compounds continue to show that rates of MACE are similar to those observed in the STELARA LTE (investigator-reported rate of 0.38 per 100 subject years of follow-up). The investigator-reported MACE rate for adalimumab was 0.36 per 100 subject years of follow-up (95% CI: 0.20, 0.59). For etanercept, Papp *et al* (Assessment of the long-term safety and effectiveness of etanercept for the treatment of psoriasis in an adult population. J Am Acad Dermatol. 2012:66(2):33-45) reported a rate for MI and stroke alone of 0.84 per 100 subject years of follow-up in the LTEs.

- The safety profile in subjects with moderate to severe psoriasis from the Asia Pacific region (Chinese subjects, [C0743T23], Korean and Taiwanese subjects [C0743T25], and Japanese subjects [JNS009-JPN-02]) was consistent with the safety profile observed in the global psoriasis studies (C0743T23 CSR, C0743T25 CSR, JNS009-JPN-02 CSR). No new ADRs were identified from these studies.
- The safety profile observed in the Phase 3b/4 CNTO1275PSO4004 (TRANSIT) study in subjects with moderate to severe psoriasis was consistent with that observed in the global psoriasis studies (CNTO1275PSO4004 CSR). No new ADRs were been identified in this study.

Clinical Studies in Other Indications

Psoriatic Arthritis

The clinical development program of STELARA for PsA included 1,073 subjects with active PsA despite previous or current DMARD and/or NSAID use). These studies demonstrated that STELARA, in dosing regimens similar to what was previously studied for psoriasis, was well-tolerated in subjects with active PsA with or without concomitant use of MTX, and the safety profile is generally consistent with that for the psoriasis studies (24W PsA). The Type II variation for the PsA indication (Stelara II-29, submitted on 04 December 2012, which received a positive opinion on 25 July 2013) included the addition of nausea and dental infections as ADRs (24W PsA). No new ADRs were identified with the additional 1-Year PsA data (Stelara II-36, submitted on 06 August 2013).

Crohn's Disease

The Phase 2 studies (C0379T07 and C0743T26) in subjects with moderately to severely active Crohn's disease demonstrated that STELARA was well tolerated when administered in IV doses up to 6 mg/kg or with SC doses up to 90 mg q8w. Ustekinumab appeared to be generally well-tolerated, both as monotherapy and in subjects receiving concomitant immunosuppression, e.g., azathioprine or 6-MP.

Multiple Sclerosis

While the maximum dose in the Phase 2 C0743T06 study provided exposure that was significantly higher than in the psoriasis population, the safety profile of STELARA in MS studies was generally consistent with the safety profile in the psoriasis studies. The program was discontinued because of lack of efficacy.

PSOLAR (Study C0168Z03) Registry Data

PSOLAR is a disease state registry designed to capture, summarize and compare data across different systemic therapies, biologic and non-biologic, available for treatment of moderate to severe psoriasis. Annual interval report analyses of PSOLAR present descriptive statistics for evaluation of safety. For all tabulations, patients are grouped according to whether they are:

- Ever (prior to or post enrolment) exposed to STELARA (STELARA Cohort);
- Ever exposed to other Sponsor biologics (i.e., infliximab and golimumab) and not to STELARA (Other Sponsor Biologic Cohort);
- Ever exposed to non-Sponsor biologics and not to STELARA, infliximab, or golimumab (Other Non-Sponsor Biologic Cohort);
- Never exposed to any biologic (No Biologic Group).

Adverse event tabulations are also presented by grouping them according to exposure to STELARA, Other Sponsor Biologics, Non-Sponsor Biologics, or No Biologics within 91 days of event onset.

Given that patients may switch between different cohort-defining therapies, the attribution of risk to a particular drug over the course of the registry can be complex and prone to potential bias. Although a patient could contribute to multiple cohorts based on medication exposure sequence, after a patient has been exposed to a given cohort-defining therapy, the duration of follow-up and AEs that occur during the follow-up period are attributed to that therapy, even if the patient is later exposed to another treatment. For patients exposed to more than one biologic agent prior to the onset of an AE, the event is assigned to only one exposure cohort based on the following hierarchical order: STELARA first, other Sponsor biologics second, other non-Sponsor biologics third, and no biologic (other psoriasis treatment) last. As noted above, the rules for attributing safety events in cases of exposure to multiple therapies are designed to "blame STELARA first" for purposes of capturing any outcome potentially related to treatment with STELARA and maximizing the likelihood of detecting any potential safety signals for STELARA.

Given that the MAH is proposing a label revision to remove the restriction to the STELARA psoriasis indication in the SmPC by establishing alignment for non-biologic step through therapy requirements with TNFα inhibitors approved for psoriasis and administered by SC injection (i.e., etanercept and adalimumab), data from the PSOLAR registry are presented to evaluate the safety profile of STELARA relative to those other therapies (i.e., Other Non-sponsor Biologic Cohort).

PSOLAR Overall Population

In 2012, the MAH submitted the yearly PSOLAR report to the EMA and CHMP, for which the CHMP concluded the following:

"The rates of all-cause mortality and major adverse cardiovascular events are generally similar in patients exposed to Stelara and other biologics and less than that observed for patients who have not received a biologic therapy. The rates of malignancies (excluding non-melanoma skin cancer) are similar across all cohorts. The rate of non-melanoma skin cancers is lower among those exposed to Stelara than those in other cohorts. The rates of serious infections and infestations are lower in the Stelara and the no biologics cohorts compared to those observed in patients exposed to other biologics. No new safety signals have been identified in patients exposed to Stelara."

The latest annual PSOLAR report was submitted on 30 January 2013 and is currently under review. For this annual safety registry report, data from 11,900 patients enrolled in PSOLAR during the

collection interval (20 June 2007 through 23 August 2012) were summarized. Of these,

- 3,796 patients were exposed to STELARA
- 1,363 were exposed to other Sponsor Biologic Therapies
- 4,492 patients were exposed to other Non-Sponsor Biologic Therapies (95% adalimumab and/or etanercept)
- 2,249 patients were receiving no biologic or were eligible to receive systemic therapies other than biologics

The total follow-up was 22,918 patient-years for the overall population, 5,332 patient-years for the Ustekinumab cohort, and 10,093 patient-years for the Non-sponsor Biologic group. At the end of the data collection interval, the median duration of follow-up for the overall population was 1.83 years, 1.52 years for the Ustekinumab cohort, and 2.00 years for the Non-sponsor Biologics Cohort.

Based on the most recent interval analysis, unadjusted rates of AE/SAEs of interest for STELARA-treated patients were generally similar to or trended lower (e.g., serious infection, malignancy) than those for patients in the Other Non-Sponsor Biologics cohort.

Incident User Cohort Analyses

The incident biologic cohorts are defined as those subsets of patients who initiated their first cohort-defining biologic at the time of or after enrolment in PSOLAR. The No Biologic Group in the incident user cohort analyses is defined as patients who never received any biologics prior to or during registry.

The incident cohort analyses were conducted to adjust for variable timing and different lengths of exposure to therapy, and to eliminate potential confounding issues for attributing safety events in the context of multiple exposures. Examination and comparison across the incident cohorts facilitates longitudinal evaluation of safety from the time therapy is initiated, thereby minimising potential biases associated with historical use or ongoing use of a given therapy initiated prior to registry enrolment, and eliminates the potential confounding related to switching therapies and exposure to multiple treatments after initiating participation in PSOLAR.

In contrast to the PSOLAR interval safety report analyses, the exposure duration for each incident biologic cohort is defined as the period between the first dose received on registry and the earlier of the date of the last dose of that cohort-defining biologic +90 days, withdrawal from the registry, initiating another biologic therapy, or the annual interval report data cut. While in the overall cohort analyses, a patient could potentially contribute exposure to all four cohorts, in the incident cohort analyses a given patient's exposure is considered only for the duration of treatment with their cohort-defining biologic, therefore allowing for each patient to be accounted for in one, unique biologic cohort. Consequently, biologic incident cohorts represent independent groups of patients, thus facilitating interpretation of comparisons among them. Patient-years is defined as the number of years the patient was ever exposed to the cohort defining biologic (Patient-years = number of days of exposure/365.25). In additional analyses, pt-yrs of exposure to STELARA or other Sponsor or non-Sponsor biologics used in these tabulations was based upon therapy administration during the study using 91-day at risk windows.

Despite the advantages of focusing analyses on the incident biologic cohorts for reducing certain biases described above, the analyses presented here are subject to several limitations. These data are derived from an observational registry and are subject to patient selection bias, reporting bias, recall bias, and other biases associated with retrospective exposure information. In addition, focusing analyses specifically on the incident biologic cohorts may limit the duration of follow up and numbers

of events factored into determining rates of events, which may limit interpretation of the data.

Furthermore, rates of AEs presented in data tables are not adjusted for differences in demographic or other characteristics among treatment groups that could potentially impact rates of safety events, in turn limiting the ability to make comparative assessments. However, adjustments for potential confounding factors were made in the Cox proportional hazards models evaluating predictors of time to first event for AEs of special of interest.

The analysis of the "incident cohorts" provides additional information on the safety of Stelara in the registry setting and the results of these analyses are detailed below. Due to the inherent limitations with both the overall cohort and incident cohort analysis, information on the safety from both is provided below.

Status through 23 August 2012

As in the most recent annual PSOLAR interval safety report, the data collection interval for the incident cohort analyses presented herein is 20 June 2007 through 23 August 2012. Table 3 provides a summary of patient disposition through 23 August 2012 for the Incident Biologic Cohorts and the No Biologic Group. Of the 11,900 patients enrolled in the registry through 23 August 2012, a total of 2,446 patients were incident users of biologic therapies (Incident Cohorts) representing 25% of the overall biologic-exposed population of patients. Among these patients, 1,454 were exposed to STELARA as first biologic in registry, 737 were exposed to other non-Sponsor biologics as first on registry biologic therapy, and 255 were similarly exposed to other Sponsor biologics (representing 38%, 16%, and 19% of the overall patients in each cohort, respectively). A total of 2,249 patients were exposed to non-biologic therapies and had never been exposed to biologic therapy prior to or during registry. The full complement of no biologic patients was considered in both the incident and overall cohort analyses.

Among the patients in the Other Non-Sponsor Biologic Incident Cohort, adalimumab and etanercept were the most common incident cohort-defining biologics, accounting for 56.6% and 40.6% of subjects in this cohort, respectively. Additional cohort-defining non-Sponsor biologics included alefacept (1.1%), efalizumab (1.1%), and other biologics (0.68%). Of patients in the Other Sponsor Biologic Incident Cohort, 86.7% were exposed to Remicade and 13.3% were exposed to Simponi.

The overall rate of discontinuation from the registry for patients included in the incident cohort analyses, 18.5% (Table 3), was similar to that for the overall cohort analyses, 16.1%. Similar to the overall STELARA Cohort, the proportion of STELARA-exposed incident cohort patients who discontinued from the registry (6.0%) was lower than that observed for the Other Non-Sponsor Biologic Incident Cohort (17.0%). In addition, the proportion of STELARA-exposed incident cohort patients who discontinued from the registry was lower than that for the Other Sponsor Biologic Incident Cohort (15.3%), and the No Biologic Group (27.4%). Among the 6.0% in the STELARA Incident Cohort who discontinued from the registry, reasons included lost or presumed lost to follow-up (40 patients), withdrawal of consent (36 patients), death (3 patients), site closing (1 patient), or other reasons (7 patients).

Table 3: Subject disposition (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454)	Other Sponsor biologic (N=255)	Other Non-Sponsor biologic (N=737)	No biologic (N=2249)	All (N=4695)
Number of patients enrolled	1454	255	737	2249	4695
Number discontinued	87 (6.0%)	39 (15.3%)	125 (17.0%)	617 (27.4%)	868 (18.5%)
Discontinuation reason					
Withdrawal of consent (patient choice)	36 (2.5%)	12 (4.7%)	41 (5.6%)	224 (10.0%)	313 (6.7%)
Inclusion / exclusion criteria not met	0	0	1 (0.1%)	0	1 (< 0.1%)
Death	3 (0.2%)	1 (0.4%)	5 (0.7%)	30 (1.3%)	39 (0.8%)
Lost to follow-up	14 (1.0%)	10 (3.9%)	38 (5.2%)	191 (8.5%)	253 (5.4%)
Presumed lost to follow-up	26 (1.8%)	15 (5.9%)	32 (4.3%)	129 (5.7%)	202 (4.3%)
Site closed	1 (0.1%)	0	2 (0.3%)	9 (0.4%)	12 (0.3%)
Other	7 (0.5%)	1 (0.4%)	6 (0.8%)	34 (1.5%)	48 (1.0%)

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab. ‘
Other Sponsor biologic’ refers to the cohort of patients whose first biologic received on registry
was (Infliximab or Golimumab). ‘
Other Non-Sponsor biologic’ refers to the cohort of patients whose first biologic received on registry was an “Other Non-Sponsor biologics”.

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Demographics

The PSOLAR study collects data on multiple characteristics of enrolled patients. Table 4 depicts the demographic features of the incident cohorts. Overall, the demographics of the incident cohorts were similar to those of the overall registry population.

Table 4: Demographics (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454)	Other Sponsor biologic (N=255)	Other Non-Sponsor biologic (N=737)	No biologic (N=2249)	All (N=4695)
Age (years)					
N	1453	255	737	2248	4693
Mean (SD)	46.08 (13.255)	47.08 (13.341)	46.58 (14.333)	50.97 (15.450)	48.55 (14.695)
Median	46.00	48.00	47.00	52.00	49.00
(Min, Max)	(18.0; 85.0)	(18.0; 80.0)	(18.0; 89.0)	(12.0; 92.0)	(12.0; 92.0)
(25%, 75%)	(36.00; 56.00)	(37.00; 56.00)	(36.00; 56.00)	(39.00; 63.00)	(37.00; 59.00)
Age Category (years)	1453	255	737	2248	4693
0-17	0	0	0	1 (< 0.1%)	1 (< 0.1%)
18-24	80 (5.5%)	12 (4.7%)	42 (5.7%)	101 (4.5%)	235 (5.0%)
25-34	214 (14.7%)	41 (16.1%)	123 (16.7%)	297 (13.2%)	675 (14.4%)
35-44	369 (25.4%)	55 (21.6%)	162 (22.0%)	378 (16.8%)	964 (20.5%)
45-54	385 (26.5%)	68 (26.7%)	188 (25.5%)	482 (21.4%)	1123 (23.9%)
55-64	284 (19.5%)	53 (20.8%)	134 (18.2%)	506 (22.5%)	977 (20.8%)
>=65	121 (8.3%)	26 (10.2%)	88 (11.9%)	483 (21.5%)	718 (15.3%)
Gender, N(%)	1454	255	737	2249	4695
Male	788 (54.2%)	141 (55.3%)	407 (55.2%)	1110 (49.4%)	2446 (52.1%)
Female	666 (45.8%)	114 (44.7%)	330 (44.8%)	1139 (50.6%)	2249 (47.9%)
Race N(%)	1454	255	736	2248	4693
White	1225 (84.3%)	221 (86.7%)	572 (77.7%)	1882 (83.7%)	3900 (83.1%)
Black	57 (3.9%)	8 (3.1%)	39 (5.3%)	86 (3.8%)	190 (4.0%)
Asian	54 (3.7%)	6 (2.4%)	43 (5.8%)	64 (2.8%)	167 (3.6%)
Hispanic or latino	89 (6.1%)	14 (5.5%)	61 (8.3%)	163 (7.3%)	327 (7.0%)
Other	29 (2.0%)	6 (2.4%)	21 (2.9%)	53 (2.4%)	109 (2.3%)
Body mass index (kg/m2)					
N	1438	253	729	2219	4639
Mean (SD)	31.634 (7.3873)	33.058 (7.8295)	30.884 (7.2777)	29.919 (6.8654)	30.774 (7.2082)
Median	30.441	32.112	29.728	28.540	29.476
(25%, 75%)	(26.649; 35.294)	(26.649; 37.768)	(25.848; 34.488)	(25.127; 33.311)	(25.770; 34.543)
(Min, Max)	(17.21; 74.41)	(19.34; 56.49)	(17.32; 65.96)	(17.22; 62.52)	(17.21; 74.41)
Obesity class N(%)	1438	253	729	2219	4639
Underweight (BMI < 18.5)	13 (0.9%)	0	3 (0.4%)	13 (0.6%)	29 (0.6%)
Normal (18.5-24.9)	224 (15.6%)	41 (16.2%)	144 (19.8%)	514 (23.2%)	923 (19.9%)
Overweight (25.0-29.9)	443 (30.8%)	62 (24.5%)	228 (31.3%)	767 (34.6%)	1500 (32.3%)
Obesity class I (30.0-34.9)	371 (25.8%)	55 (21.7%)	190 (26.1%)	494 (22.3%)	1110 (23.9%)
Obesity class II (35.0-39.9)	205 (14.3%)	43 (17.0%)	91 (12.5%)	230 (10.4%)	569 (12.3%)
Obesity class III (40.0 +)	182 (12.7%)	52 (20.6%)	73 (10.0%)	201 (9.1%)	508 (11.0%)

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
‘Other Sponsor biologic’ refers to the cohortof patients whose first biologic received on registry was (Infliximab or Golimumab)
. ‘Other Non-Sponsor biologic’ refers to the cohort of patients whose first biologic received on registry was an “
Other Non-Sponsor biologics”.
Obesity class based upon National Heart Lung and Blood Institute Obesity Education Initiative -
http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.html

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Key: BMI=body mass index; Min, Max=minimum, maximum; SD=Standard deviation

Medical History

Median time since psoriasis diagnosis in the incident cohort analyses (12.1 years, Table 5) was slightly lower than that observed for the overall cohort analyses (15.2 years). As in the overall cohort analyses features of medical history were generally similar across treatment groups in the incident cohort analyses (Table 5).

Table 5: Medical history (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454)	Other Sponsor biologic (N=255)	Other Non-Sponsor biologic (N=737)	No biologic (N=2249)	All (N=4695)
Years since psoriasis Dx					
N	1445	252	732	2226	4655
Mean (SD)	18.588 (12.8712)	15.611 (11.7388)	12.605 (12.2636)	14.346 (14.5375)	15.458 (13.7262)
Median	17.049	14.123	8.252	9.969	12.077
(Min, Max)	(0.00; 62.74)	(0.00; 50.29)	(0.00; 60.87)	(0.00; 73.05)	(0.00; 73.05)
(25%, 75%)	(8.329; 26.724)	(5.165; 23.472)	(2.225; 20.167)	(2.256; 22.026)	(3.775; 23.819)
Patients with psoriatic arthritis N(%)	554 (38.1%)	131 (51.4%)	233 (31.6%)	409 (18.2%)	1327 (28.3%)
Number of patients with medical history data	1453	255	737	2243	4688
Cardiovascular	548 (37.7%)	110 (43.1%)	258 (35.0%)	842 (37.5%)	1758 (37.5%)
Atherosclerotic disease	39 (2.7%)	10 (3.9%)	22 (3.0%)	81 (3.6%)	152 (3.2%)
Peripheral arterial disease	3 (0.2%)	2 (0.8%)	9 (1.2%)	14 (0.6%)	28 (0.6%)
Coronary artery disease	34 (2.3%)	8 (3.1%)	13 (1.8%)	69 (3.1%)	124 (2.6%)
Transient ischemic attack/CVA/stroke	15 (1.0%)	2 (0.8%)	6 (0.8%)	38 (1.7%)	61 (1.3%)
Angina	10 (0.7%)	2 (0.8%)	10 (1.4%)	36 (1.6%)	58 (1.2%)
Congestive heart failure	14 (1.0%)	4 (1.6%)	4 (0.5%)	28 (1.2%)	50 (1.1%)
Myocardial infarction	32 (2.2%)	5 (2.0%)	15 (2.0%)	68 (3.0%)	120 (2.6%)
Hypertension	413 (28.4%)	87 (34.1%)	204 (27.7%)	635 (28.3%)	1339 (28.6%)
Hyperlipidemia	277 (19.1%)	57 (22.4%)	109 (14.8%)	410 (18.3%)	853 (18.2%)
Pulmonary	210 (14.5%)	46 (18.0%)	98 (13.3%)	339 (15.1%)	693 (14.8%)
Sleep apnea	83 (5.7%)	17 (6.7%)	34 (4.6%)	111 (4.9%)	245 (5.2%)
Asthma	110 (7.6%)	23 (9.0%)	54 (7.3%)	200 (8.9%)	387 (8.3%)
Chronic obstructive pulmonary disease	28 (1.9%)	5 (2.0%)	12 (1.6%)	54 (2.4%)	99 (2.1%)
Pneumonitis	2 (0.1%)	4 (1.6%)	2 (0.3%)	15 (0.7%)	23 (0.5%)
Psychiatric illness	312 (21.5%)	65 (25.5%)	151 (20.5%)	440 (19.6%)	968 (20.6%)
Anxiety	164 (11.3%)	27 (10.6%)	88 (11.9%)	236 (10.5%)	515 (11.0%)
Depression	220 (15.1%)	56 (22.0%)	96 (13.0%)	317 (14.1%)	689 (14.7%)
Suicidal ideation	9 (0.6%)	4 (1.6%)	7 (0.9%)	24 (1.1%)	44 (0.9%)
Bipolar	19 (1.3%)	5 (2.0%)	13 (1.8%)	31 (1.4%)	68 (1.5%)
Schizophrenia	4 (0.3%)	1 (0.4%)	1 (0.1%)	5 (0.2%)	11 (0.2%)
Hepatic	75 (5.2%)	14 (5.5%)	25 (3.4%)	72 (3.2%)	186 (4.0%)
Hep B	7 (0.5%)	1 (0.4%)	3 (0.4%)	13 (0.6%)	24 (0.5%)
Hep C	16 (1.1%)	4 (1.6%)	13 (1.8%)	23 (1.0%)	56 (1.2%)
Alcoholic	2 (0.1%)	2 (0.8%)	3 (0.4%)	6 (0.3%)	13 (0.3%)
Idiopathic/autoimmune	4 (0.3%)	2 (0.8%)	1 (0.1%)	4 (0.2%)	11 (0.2%)
Drug induced (psoriasis treatment med / other)	11 (0.8%)	1 (0.4%)	1 (0.1%)	13 (0.6%)	26 (0.6%)
Cirrhosis	11 (0.8%)	2 (0.8%)	6 (0.8%)	11 (0.5%)	30 (0.6%)
Liver biopsy	44 (3.0%)	5 (2.0%)	6 (0.8%)	22 (1.0%)	77 (1.6%)
Skin cancer	65 (4.5%)	20 (7.8%)	30 (4.1%)	173 (7.7%)	288 (6.1%)
Basal cell carcinoma	42 (2.9%)	15 (5.9%)	16 (2.2%)	101 (4.5%)	174 (3.7%)
Squamous cell carcinoma	25 (1.7%)	4 (1.6%)	9 (1.2%)	67 (3.0%)	105 (2.2%)
Melanoma	9 (0.6%)	4 (1.6%)	3 (0.4%)	23 (1.0%)	39 (0.8%)
Unknown skin cancer	2 (0.1%)	1 (0.4%)	2 (0.3%)	17 (0.8%)	22 (0.5%)
Other types of Cancer	40 (2.8%)	2 (0.8%)	22 (3.0%)	147 (6.6%)	211 (4.5%)
Endocrine	258 (17.8%)	51 (20.0%)	119 (16.1%)	467 (20.8%)	895 (19.1%)
Diabetes mellitus type I	22 (1.5%)	4 (1.6%)	13 (1.8%)	25 (1.1%)	64 (1.4%)
Diabetes mellitus type II	161 (11.1%)	29 (11.4%)	74 (10.0%)	260 (11.6%)	524 (11.2%)
Thyroid dysfunction	99 (6.8%)	24 (9.4%)	42 (5.7%)	220 (9.8%)	385 (8.2%)
Other disease	408 (28.1%)	81 (31.8%)	187 (25.4%)	629 (28.0%)	1305 (27.8%)
Inflammatory bowel disease	23 (1.6%)	5 (2.0%)	8 (1.1%)	54 (2.4%)	90 (1.9%)
Crohn's disease	4 (0.3%)	0	2 (0.3%)	7 (0.3%)	13 (0.3%)
Ulcerative colitis	11 (0.8%)	3 (1.2%)	1 (0.1%)	16 (0.7%)	31 (0.7%)
Indeterminate colitis	7 (0.5%)	2 (0.8%)	4 (0.5%)	32 (1.4%)	45 (1.0%)
Demyelinating disease	5 (0.3%)	0	0	6 (0.3%)	11 (0.2%)
Multiple sclerosis	4 (0.3%)	0	0	6 (0.3%)	10 (0.2%)
Optic neuritis	1 (0.1%)	0	0	0	1 (< 0.1%)
Bone marrow suppression	0	0	0	1 (< 0.1%)	1 (< 0.1%)
Environmental allergy	124 (8.5%)	20 (7.8%)	67 (9.1%)	194 (8.6%)	405 (8.6%)
Drug allergy	314 (21.6%)	68 (26.7%)	140 (19.0%)	479 (21.4%)	1001 (21.4%)
Lupus	7 (0.5%)	0	2 (0.3%)	7 (0.3%)	16 (0.3%)

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab. ‘
‘Other Sponsor biologic’ refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab). ‘
‘Other Non-Sponsor biologic’ refers to the cohort of patients whose first biologic received on registry was an “Other Non-Sponsor biologics”.

Social History

As for the overall cohort analyses, histories of alcohol use and smoking were generally similar across treatment groups in the incident cohort analyses.

Psoriasis Medication History

Table 6 shows general psoriasis medication history for the incident cohort analyses. In general, psoriasis medication history for the incident cohort analyses was similar to that for the overall cohort analyses.

Across treatment groups, 93.9% of patients had previously received topical steroid therapy (Table 6). The STELARA Incident Cohort had a higher proportion of patients that had received phototherapy (62.0%) relative to the Other Non-Sponsor Biologic Incident Cohort (39.1%), as well as the Other Sponsor Biologic Incident Cohort (52.8%) and the No Biologic Group (45.8%). Similarly, the STELARA Incident Cohort had a higher proportion of patients that had received cyclosporine (25.5%) than the Other Non-Sponsor Biologic Incident Cohort (10.7%), as well as the Other Sponsor Biologic Incident Cohort (20.9%) and the No Biologic Group (3.6%).

Table 6: Psoriasis medication history (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454)	Other Sponsor biologic (N=255)	Other Non-Sponsor biologic (N=737)	No biologic (N=2249)	All (N=4695)
Number of patients with data	1450	254	736	2238	4678
Topical therapy	1404 (96.8%)	247 (97.2%)	717 (97.4%)	2135 (95.4%)	4503 (96.3%)
Topical steroid therapy	1398 (96.4%)	244 (96.1%)	695 (94.4%)	2056 (91.9%)	4393 (93.9%)
High potency	1206 (83.2%)	208 (81.9%)	579 (78.7%)	1646 (73.5%)	3639 (77.8%)
Medium potency	966 (66.6%)	152 (59.8%)	413 (56.1%)	1140 (50.9%)	2671 (57.1%)
Low potency	630 (43.4%)	101 (39.8%)	246 (33.4%)	725 (32.4%)	1702 (36.4%)
Photo therapy	899 (62.0%)	134 (52.8%)	288 (39.1%)	1024 (45.8%)	2345 (50.1%)
Psoralens + UVA	303 (20.9%)	51 (20.1%)	88 (12.0%)	193 (8.6%)	635 (13.6%)
UVB	764 (52.7%)	111 (43.7%)	246 (33.4%)	896 (40.0%)	2017 (43.1%)
Laser	13 (0.9%)	1 (0.4%)	9 (1.2%)	47 (2.1%)	70 (1.5%)
Systemic steroids	358 (24.7%)	71 (28.0%)	158 (21.5%)	458 (20.5%)	1045 (22.3%)
Retinoids and/or combination topical	723 (49.9%)	118 (46.5%)	289 (39.3%)	722 (32.3%)	1852 (39.6%)
Acitretin	391 (27.0%)	55 (21.7%)	109 (14.8%)	247 (11.0%)	802 (17.1%)
Etretinate	16 (1.1%)	3 (1.2%)	3 (0.4%)	7 (0.3%)	29 (0.6%)
Tazorac	183 (12.6%)	29 (11.4%)	61 (8.3%)	165 (7.4%)	438 (9.4%)
Taclonex	363 (25.0%)	64 (25.2%)	186 (25.3%)	470 (21.0%)	1083 (23.2%)
Immunomodulators	806 (55.6%)	159 (62.6%)	269 (36.5%)	605 (27.0%)	1839 (39.3%)
Cyclosporine	370 (25.5%)	53 (20.9%)	79 (10.7%)	81 (3.6%)	583 (12.5%)
Methotrexate	657 (45.3%)	133 (52.4%)	217 (29.5%)	524 (23.4%)	1531 (32.7%)
Oral Tacrolimus	2 (0.1%)	0	0	2 (0.1%)	4 (0.1%)
Mycophenolate mofetil	15 (1.0%)	0	1 (0.1%)	3 (0.1%)	19 (0.4%)
Other Immunomodulators	46 (3.2%)	4 (1.6%)	11 (1.5%)	36 (1.6%)	97 (2.1%)
Number of Patients with NSAID data	1453	255	736	2241	4685
NSAIDs	289 (19.9%)	73 (28.6%)	116 (15.8%)	255 (11.4%)	733 (15.6%)
Sulfasalazine	25 (1.7%)	2 (0.8%)	5 (0.7%)	18 (0.8%)	50 (1.1%)
Other NSAIDs	275 (18.9%)	72 (28.2%)	112 (15.2%)	243 (10.8%)	702 (15.0%)

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".

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Key: NSAIDs=nonsteroidal anti-inflammatory drugs; UV=ultraviolet light

Table 7 lists history of exposure to biologic medications. The proportion of patients previously treated with a biologic was higher for the STELARA Incident Cohort (75.8%) than the Other Non-Sponsor Biologic Incident Cohort (10.0%). The Other Sponsor Biologic Incident Cohort had the highest proportion of patients previously treated with a biologic (79.2%). Among patients in the STELARA Incident Cohort, 52.7% were previously exposed to etanercept, 38.6% were exposed to adalimumab, and 20.1% were exposed to Remicade. A total of 42.4% of STELARA, 0.5% of Other Non-Sponsor Biologic, and 40.8% of Other Sponsor Biologic Incident Cohort patients had received ⩾2 other biologic therapies.

Table 7: Biologic medication history at entry (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454)	Other Sponsor biologic (N=255)	Other Non-Sponsor biologic (N=737)	No biologic (N=2249)	All (N=4695)
Any biologic medication	1102 (75.8%)	202 (79.2%)	74 (10.0%)	0	1378 (29.4%)
History of biologic medications at entry					
Infliximab (Remicade)	292 (20.1%)	0	54 (7.3%)	0	346 (7.4%)
Ustekinumab (Stelara)	0	33 (12.9%)	24 (3.3%)	0	57 (1.2%)
Golimumab (Simponi)	14 (1.0%)	0	0	0	14 (0.3%)
Adalimumab (Humira)	561 (38.6%)	126 (49.4%)	0	0	687 (14.6%)
Alefacept (Amevive)	132 (9.1%)	10 (3.9%)	0	0	142 (3.0%)
Efalizumab (Raptiva)	246 (16.9%)	39 (15.3%)	0	0	285 (6.1%)
Etanercept (Enbrel)	766 (52.7%)	130 (51.0%)	0	0	896 (19.1%)
Other	32 (2.2%)	4 (1.6%)	0	0	36 (0.8%)
Number of biologic medications used prior to entry					
0	352 (24.2%)	53 (20.8%)	663 (90.0%)	2249 (100.0%)	3317 (70.6%)
1	486 (33.4%)	98 (38.4%)	70 (9.5%)	0	654 (13.9%)
2	372 (25.6%)	79 (31.0%)	4 (0.5%)	0	455 (9.7%)
3	175 (12.0%)	16 (6.3%)	0	0	191 (4.1%)
4	58 (4.0%)	7 (2.7%)	0	0	65 (1.4%)
5	10 (0.7%)	2 (0.8%)	0	0	12 (0.3%)
6	1 (0.1%)	0	0	0	1 (0.0%)

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".

Infection History

Table 8 shows the proportions of patients with a history of significant infection requiring treatment within the 3 years prior to enrolment in PSOLAR. The proportion of patients with a history of significant infection in the incident cohort analyses (23.4%) was similar to that observed for the overall cohort analyses (24.6%). The proportion of patients reporting a prior history of significant infection was higher for the STELARA Incident Cohort (25.2%) than for the Other Non-Sponsor Biologic Incident Cohort (23.1%). The percentage reporting a history of significant infections was 31% in the Other Sponsor Incident Cohort and 21.4% in the No Biologic Group.

Table 8: Infection history (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454)	Other Sponsor biologic (N=255)	Other Non-Sponsor biologic (N=737)	No biologic (N=2249)	All (N=4695)
Number of patients with data	1454	255	737	2243	4689
Significant infections requiring Rx within 3 years	366 (25.2%)	79 (31%)	170 (23.1%)	481 (21.4%)	1096 (23.4%)
Opportunistic infection	24 (1.7%)	1 (0.4%)	10 (1.4%)	27 (1.2%)	62 (1.3%)
Viral infection	41 (2.8%)	6 (2.4%)	17 (2.3%)	49 (2.2%)	113 (2.4%)
Bacterial infection	325 (22.4%)	73 (28.6%)	152 (20.6%)	427 (19%)	977 (20.8%)
Hospitalization	60 (4.1%)	16 (6.3%)	22 (3%)	105 (4.7%)	203 (4.3%)

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".

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Key: Rx=treatment

Historical Peak Activity and Baseline Disease Status

Table 9 lists peak historical disease activity data available to investigative sites at enrolment. Median time since highest degree of disease activity in the incident cohort analyses was shorter (0.52 years) compared with the overall cohort analyses (1.35 years). Median time since highest degree of disease activity was longer for the STELARA Incident Cohort (0.97 years) than for the Other Non-Sponsor Biologic Incident Cohort (0.23 years), as well as for the Other Sponsor Biologic Incident Cohort (0.80 years) and the No Biologic Group (0.45 years). In contrast, median time since highest degree of disease activity was generally similar among biologic cohorts in the overall cohort analyses (STELARA: 1.67 years; Other Non-Sponsor Biologic: 1.49 years; Other Sponsor Biologic: 1.97 years) and longer compared to the No Biologic Group (0.45 years). Median body surface area (BSA) at peak activity in

both the incident (Table 9) and overall cohort analyses was 20.0%. Median BSA at peak activity was higher in the STELARA Incident Cohort (27.0%) compared with the Other Non-Sponsor Biologic Incident Cohort (20.0%). Median BSA at peak activity was 26.0% for the Other Sponsor Biologic Incident Cohort and 15.0% for the No Biologic Group. Median peak Physician's Global Assessment (PGA) score at peak activity was 3.00 in both the incident and overall cohort analyses. The proportion of patients with a peak PGA score of 4 or 5 was 38.8% for the STELARA Incident Cohort compared with 31.0% for the Other Non-Sponsor Biologic Incident Cohort. The Other Sponsor Biologic Incident Cohort had the highest proportion of patients with a peak PGA score of 4 or 5 (42.0%) and the No Biologic Group had the lowest proportion (26.6%).

Table 9: Historical peak disease activity (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454)	Other Sponsor biologic (N=255)	Other Non-Sponsor biologic (N=737)	No biologic (N=2249)	All (N=4695)
Number of patients with data	1049	179	547	1459	3234
Time since highest degree of disease activity (years)					
N	1049	179	547	1459	3234
Mean (SD)	2.92 (5.545)	2.51 (4.367)	1.45 (3.428)	2.48 (5.956)	2.45 (5.408)
Median	0.97	0.80	0.23	0.45	0.52
(Min, Max)	(0.0; 56.7)	(0.0; 26.8)	(0.0; 29.7)	(0.0; 71.3)	(0.0; 71.3)
(25%, 75%)	(0.15; 3.50)	(0.15; 2.94)	(0.03; 1.06)	(0.06; 2.02)	(0.07; 2.35)
Systemic therapy at peak activity	425 (40.5%)	74 (41.3%)	121 (22.1%)	325 (22.3%)	945 (29.2%)
Psoralens + UVA	18 (1.7%)	6 (3.4%)	8 (1.5%)	24 (1.6%)	56 (1.7%)
UVB	75 (7.1%)	13 (7.3%)	38 (6.9%)	169 (11.6%)	295 (9.1%)
Oral tacrolimus	0	0	0	1 (0.1%)	1 (< 0.1%)
Mycophenolate mofetil	0	0	0	0	0
Sulfasalazine	2 (0.2%)	0	0	4 (0.3%)	6 (0.2%)
Retinoids	44 (4.2%)	5 (2.8%)	36 (6.6%)	53 (3.6%)	138 (4.3%)
Acitretin (Soriatane)	40 (3.8%)	5 (2.8%)	15 (2.7%)	44 (3.0%)	104 (3.2%)
Cyclosporine	38 (3.6%)	6 (3.4%)	11 (2.0%)	7 (0.5%)	62 (1.9%)
Methotrexate	82 (7.8%)	11 (6.1%)	26 (4.8%)	67 (4.6%)	186 (5.8%)
Other immunomodulators	3 (0.3%)	2 (1.1%)	2 (0.4%)	6 (0.4%)	13 (0.4%)
Adalimumab (Humira)	69 (6.6%)	18 (10.1%)	5 (0.9%)	0	92 (2.8%)
Alefacept (Amevive)	10 (1.0%)	0	0	0	10 (0.3%)
Efalizumab (Raptiva)	29 (2.8%)	7 (3.9%)	0	0	36 (1.1%)
Etanercept (Enbrel)	107 (10.2%)	19 (10.6%)	9 (1.6%)	0	135 (4.2%)
Infliximab (Remicade)	24 (2.3%)	2 (1.1%)	8 (1.5%)	0	34 (1.1%)
Ustekinumab (Stelara)	7 (0.7%)	1 (0.6%)	2 (0.4%)	0	10 (0.3%)
Golimumab (Simponi)	1 (0.1%)	1 (0.6%)	0	0	2 (0.1%)
BSA at peak activity by palm method (%)					
N	851	145	462	1240	2698
Mean (SD)	36.06 (26.543)	32.83 (25.072)	26.79 (23.940)	22.55 (22.088)	28.09 (24.766)
Median	27.00	26.00	20.00	15.00	20.00
(Min, Max)	(0.0; 100.0)	(1.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)
(25%, 75%)	(15.00; 51.00)	(12.00; 50.00)	(10.00; 40.00)	(7.00; 30.00)	(10.00; 40.00)
PGA score at peak activity					
N	856	145	464	1250	2715
Mean (SD)	3.28 (0.946)	3.26 (0.896)	3.09 (0.982)	2.96 (0.955)	3.10 (0.964)
Median	3.00	3.00	3.00	3.00	3.00
(Min, Max)	(0.0; 5.0)	(0.0; 5.0)	(0.0; 5.0)	(0.0; 5.0)	(0.0; 5.0)
(25%, 75%)	(3.00; 4.00)	(3.00; 4.00)	(3.00; 4.00)	(2.00; 4.00)	(3.00; 4.00)
PGA score at peak activity					
0 - clear	17 (2.0%)	3 (2.1%)	5 (1.1%)	12 (1.0%)	37 (1.4%)
1 - minimal	13 (1.5%)	1 (0.7%)	21 (4.5%)	68 (5.4%)	103 (3.8%)
2 - mild	87 (10.2%)	18 (12.4%)	78 (16.8%)	265 (21.2%)	448 (16.5%)
3 - moderate	407 (47.5%)	62 (42.8%)	216 (46.6%)	573 (45.8%)	1258 (46.3%)
4 - marked	263 (30.7%)	56 (38.6%)	111 (23.9%)	277 (22.2%)	707 (26.0%)
5 - severe	69 (8.1%)	5 (3.4%)	33 (7.1%)	55 (4.4%)	162 (6.0%)

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".

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Key: BSA=body surface area; Min,Max=minimum, maximum; PGA=Physician's Global Assessment; SD=standard deviation; UV=ultraviolet light

In order to provide the context of disease activity at entry, PSOLAR also collects information on baseline disease activity (Table 10). Baseline disease activity in the incident cohort analyses was generally similar to that in the overall cohort analyses. In the incident cohort analyses (Table 10), the

vast majority of patients had plaque psoriasis (⩾95.0%). No clinically relevant differences in median baseline BSA measured by the palm method (10.0%), median baseline PGA score (3.0), or baseline PGA score distribution were observed across incident biologic cohorts. Median baseline BSA (7.0%) and median baseline PGA score (2.0) were lower for the No Biologic Group compared with the incident biologic cohorts.

Table 10: Baseline physician global assessment and psoriasis diagnoses (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454)	Other Sponsor biologic (N=255)	Other Non-Sponsor biologic (N=737)	No biologic (N=2249)	All (N=4695)
Number of patients with data	1451	254	735	2238	4678
Psoriasis Type					
Plaque	1429 (98.5%)	251 (98.8%)	706 (96.1%)	2126 (95.0%)	4512 (96.5%)
Other	159 (10.9%)	28 (11%)	81 (11%)	258 (11.5%)	526 (11.2%)
BSA by palm method (%)					
N	1436	251	730	2232	4649
Mean (SD)	18.6 (20.88)	19.9 (22.10)	18.5 (20.85)	13.7 (17.40)	16.3 (19.52)
Median	10.0	10.0	10.0	7.0	10.0
IQ range	(4.3; 25.0)	(4.0; 30.0)	(5.0; 25.0)	(3.0; 17.0)	(3.2; 20.0)
Range	(0; 100)	(0; 90)	(0; 99)	(0; 100)	(0; 100)
PGA Score					
N	1420	250	701	2104	4475
Mean (SD)	2.6 (1.13)	2.7 (1.12)	2.6 (1.09)	2.3 (1.09)	2.4 (1.11)
Median	3.0	3.0	3.0	2.0	3.0
IQ range	(2.0; 3.0)	(2.0; 3.0)	(2.0; 3.0)	(2.0; 3.0)	(2.0; 3.0)
Range	(0; 5)	(0; 5)	(0; 5)	(0; 5)	(0; 5)
PGA score distribution	1420	250	701	2104	4475
0 - clear	55 (3.9%)	10 (4.0%)	25 (3.6%)	99 (4.7%)	189 (4.2%)
1 - minimal	205 (14.4%)	28 (11.2%)	75 (10.7%)	404 (19.2%)	712 (15.9%)
2 - mild	368 (25.9%)	63 (25.2%)	188 (26.8%)	665 (31.6%)	1284 (28.7%)
3 - moderate	524 (36.9%)	90 (36.0%)	288 (41.1%)	709 (33.7%)	1611 (36.0%)
4 - marked	223 (15.7%)	54 (21.6%)	94 (13.4%)	179 (8.5%)	550 (12.3%)
5 - severe	45 (3.2%)	5 (2.0%)	31 (4.4%)	48 (2.3%)	129 (2.9%)

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".

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Key: BSA=body surface area; IQ=interquartile; PGA=Physician's global assessment; SD=standard deviation

Adverse Events

The PSOLAR study collects data on AEs that may be classified as follows: non-serious AEs related to the treatment of psoriasis, SAEs, and AEs of special interest. Data on non-serious AEs are collected at each patients 6-month interval registry visit; thus, capture of a non-serious AE within the PSOLAR database may lag behind the actual time of onset. Serious adverse events and AEs of special interest are reported and evaluated on an ongoing basis.

Exposure

Table 11 provides data on exposure to therapy for each incident biologic cohort and overall exposure for the No Biologic Group. Patient-years of follow up for the incident cohort analyses represent about 31% (7,021/22,918) of the overall pt-yrs of follow up accrued through the data cut. However, pt-yrs of exposure specifically for the biologic incident cohorts were only about 16% (2,942/18,561) of those accrued for the overall biologic cohorts. The STELARA Incident Cohort had 1,666 pt-yrs of exposure compared with 992 pt-yrs for the Other Non-Sponsor Biologic Incident Cohort. The Other Sponsor Biologic Incident Cohort had 284 pt-yrs of exposure and the No Biologic Group had 4,079 pt-yrs of exposure. Median exposure was 0.99 years for the STELARA Incident Cohort and 1.08 years for the Other Non-Sponsor Incident Cohort. For the Other Sponsor Biologic Incident Cohort and the No Biologic Group, median exposures were 0.84 years and 1.71 years, respectively. The limited number

of pt-yrs of exposure for the Other Sponsor Biologic Incident Cohort should be considered when evaluating the safety data presented below.

Table 11: Exposure in incident cohort

	Ustekinumab (N=1454)	Other Sponsor Biologic (N=255)	Other Non-Sponsor Biologic (N=737)	No Biologic (N=2249)	All (N=4695)
Patient-years[a]	1666	284	992	4079	7021
Mean (standard deviation), years	1.15 (0.798)	1.11 (0.846)	1.35 (1.001)	1.81 (1.102)	1.50 (1.036)
Median, years	0.99	0.84	1.08	1.71	1.27
Range	(0.0; 3.3)	(0.0; 4.3)	(0.0; 4.8)	(0.0; 5.1)	(0.0; 5.1)
Interquartile range	(0.48; 1.75)	(0.50; 1.58)	(0.58; 1.97)	(0.90; 2.59)	(0.64; 2.23)

N=number of patients
Note: Patient-years is defined as the number of years the patients were exposed to the cohort defining biologic. (Patient-years = number of days of exposure / 365.25).

All Adverse Events

Table 12 reflects the cumulative incidence of AEs by system organ class with rates per 100 pt-yrs. The AE profile in the incident cohort analyses was generally similar to that for the overall cohort analyses. The rate of overall AEs across all treatment groups was 24.26 per 100 pt-yrs in the incident cohort analyses and 25.39 per 100 pt-yrs in the overall cohort analyses. The rate of overall AEs in the STELARA Incident Cohort was 25.99 per 100 pt-yrs, compared to 27.62 per 100 pt-yrs for the Other Non-Sponsor Biologic Incident Cohort. The overall rate of AEs was highest for the Other Sponsor Biologic Incident Cohort (58.1 per 100 pt-yrs) and lowest for the No Biologic Group (20.37 per 100 pt-yrs). Rates of AEs among each treatment group in the incident cohort analyses generally reflect those observed for each group in the overall cohort analyses (STELARA: 20.72; Other Non-Sponsor Biologic: 26.58; Other Sponsor Biologic: 36.42; and No Biologic: 20.40 per 100 pt-yrs).

The rates of infections and infestations were 9.66 per 100 pt-yrs for the STELARA and 11.79 per 100 pt-yrs for the Other Non-Sponsor Biologic Incident Cohorts (Table 12). In the incident cohort analyses, the Other Sponsor Biologic Incident Cohort had the highest rate of infections and infestations (13.73 per 100 pt-yrs) and the No Biologic Group had the lowest rate (5.47 per 100 pt-yrs). These rates also generally reflect rates of infections and infestations for each treatment group in the overall cohort analyses (STELARA: 7.24 per 100 pt-yrs; Other Non-Sponsor Biologic: 8.8 per 100 pt-yrs; Other Sponsor Biologic: 12.98 per 100 pt-yrs; and No Biologic: 5.53 per 100 pt-yrs).

The rate of neoplasms (aggregate) was lower (1.26 per 100 pt-yrs) for the STELARA Incident Cohort compared with the Other Non-Sponsor Biologic Incident Cohort (1.51 per 100 pt-yrs, Table 12). The rates of neoplasms were higher for both the Other Sponsor Biologic Incident Cohort (2.46 per 100 pt-yrs) and the No Biologic Group (3.26 per 100 pt-yrs). Similarly, these rates generally reflect those for neoplasms in the overall cohort analyses (STELARA: 1.63 per 100 pt-yrs; Other Sponsor Biologic: 2.46 per 100 pt-yrs; No Biologic: 3.12 per 100 pt-yrs), although the rate for the overall Other Non-Sponsor Biologic Cohort (2.84 per 100 pt-yrs) is somewhat higher compared with the rate for the incident cohort (1.51 per 100 pt-yrs).

The rates of cardiac disorders for the STELARA and Other Non-Sponsor Biologic Incident Cohorts were similar (1.62 per 100 pt-yrs and 1.61 per 100 pt-yrs, respectively, Table 12). In the incident cohort analyses, the rate of cardiac disorders was highest for the Other Sponsor Biologic Incident Cohort (2.46 per 100 pt-yrs) and lowest for the No Biologic Group (1.37 per 100 pt-yrs). Rates of cardiac disorders were generally more comparable across treatment groups in the overall cohort analyses (STELARA: 1.05 per 100 pt-yrs; Other Non-Sponsor Biologic: 0.94 per 100 pt-yrs; Other Sponsor Biologic: 1.53 per 100 pt-yrs; and No Biologic: 1.31 per 100 pt-yrs).

Table 12: Cumulative incidence rates of adverse events per 100 patient-years (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1666 Pt-Yrs)	Other Sponsor biologic (N=284 Pt-Yrs)	Other Non-Sponsor biologic (N=993 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=7022 Pt-Yrs)
All events	25.99 [433]	58.1 [165]	27.59 [274]	20.37 [831]	24.25 [1703]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0.24 [4]	0.7 [2]	0.81 [8]	0.47 [19]	0.47 [33]
CARDIAC DISORDERS	1.62 [27]	2.46 [7]	1.61 [16]	1.37 [56]	1.51 [106]
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0.12 [2]	0.00 [0]	0.00 [0]	0.05 [2]	0.06 [4]
EAR AND LABYRINTH DISORDERS	0.12 [2]	0.35 [1]	0.00 [0]	0.05 [2]	0.07 [5]
ENDOCRINE DISORDERS	0.06 [1]	0.00 [0]	0.00 [0]	0.1 [4]	0.07 [5]
EYE DISORDERS	0.36 [6]	0.00 [0]	0.2 [2]	0.2 [8]	0.23 [16]
GASTROINTESTINAL DISORDERS	0.84 [14]	2.11 [6]	0.91 [9]	0.98 [40]	0.98 [69]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0.96 [16]	2.46 [7]	1.51 [15]	0.54 [22]	0.85 [60]
HEPATOBILIARY DISORDERS	0.42 [7]	0.35 [1]	0.4 [4]	0.25 [10]	0.31 [22]
IMMUNE SYSTEM DISORDERS	0.24 [4]	2.11 [6]	0.4 [4]	0.17 [7]	0.3 [21]
INFECTIONS AND INFESTATIONS	9.66 [161]	13.73 [39]	11.78 [117]	5.47 [223]	7.69 [540]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0.72 [12]	3.17 [9]	0.1 [1]	1.25 [51]	1.04 [73]
INVESTIGATIONS	1.02 [17]	3.17 [9]	0.4 [4]	0.56 [23]	0.75 [53]
METABOLISM AND NUTRITION DISORDERS	0.72 [12]	1.41 [4]	0.5 [5]	0.59 [24]	0.64 [45]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1.38 [23]	5.63 [16]	2.01 [20]	1.1 [45]	1.48 [104]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1.26 [21]	2.46 [7]	1.51 [15]	3.26 [133]	2.51 [176]
NERVOUS SYSTEM DISORDERS	1.5 [25]	4.93 [14]	0.81 [8]	0.74 [30]	1.1 [77]
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0.12 [2]	0.00 [0]	0.7 [7]	0.1 [4]	0.19 [13]
PSYCHIATRIC DISORDERS	0.42 [7]	1.06 [3]	0.4 [4]	0.37 [15]	0.41 [29]
RENAL AND URINARY DISORDERS	0.36 [6]	1.06 [3]	0.2 [2]	0.66 [27]	0.54 [38]
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0.12 [2]	1.06 [3]	0.1 [1]	0.2 [8]	0.2 [14]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1.38 [23]	3.52 [10]	0.5 [5]	0.42 [17]	0.78 [55]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1.38 [23]	5.28 [15]	1.41 [14]	0.66 [27]	1.13 [79]
SOCIAL CIRCUMSTANCES	0.00 [0]	0.00 [0]	0.1 [1]	0.00 [0]	0.01 [1]
SURGICAL AND MEDICAL PROCEDURES	0.36 [6]	0.35 [1]	0.2 [2]	0.37 [15]	0.34 [24]
VASCULAR DISORDERS	0.54 [9]	0.7 [2]	1.01 [10]	0.47 [19]	0.57 [40]

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".
The incidence of adverse events is reported as rate of adverse events per 100 patient-years.
Patient-years is defined as the number of years the patients exposed to the cohort defining biologic.
(Patient-years = number of days of exposure / 365.25).

No signal for cardiac AEs with Stelara was noted as compared with other biologic cohorts, although the rate of cardiac AEs was higher in all biologics cohorts as compared with the non-biologic cohort. Of note, the biologics cohorts had more severe disease overall at peak activity than the non-biologic cohort and were also more obese, in particular the Stelara cohort.

In the incident cohort analyses, overall rates of AEs per 100 pt-yrs using 91-day at risk windows were generally similar to those observed for AEs based on any exposure prior to the event (Table 13).

Table 13: Cumulative incidence rates of adverse events within 91 days of biologic administration per 100 patient-years by system organ class (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454 Pt-Yrs)	Other Sponsor biologic (N=261 Pt-Yrs)	Other Non-Sponsor biologic (N=956 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=6750 Pt-Yrs)
All events	24.21 [352]	63.60 [166]	27.82 [266]	20.47 [835]	23.99 [1619]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0.28 [4]	0.77 [2]	0.73 [7]	0.47 [19]	0.47 [32]
CARDIAC DISORDERS	1.51 [22]	2.68 [7]	1.57 [15]	1.37 [56]	1.48 [100]
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0.14 [2]	0.00 [0]	0.00 [0]	0.07 [3]	0.07 [5]
EAR AND LABYRINTH DISORDERS	0.14 [2]	0.38 [1]	0.00 [0]	0.05 [2]	0.07 [5]
ENDOCRINE DISORDERS	0.07 [1]	0.00 [0]	0.00 [0]	0.10 [4]	0.07 [5]
EYE DISORDERS	0.14 [2]	0.00 [0]	0.21 [2]	0.20 [8]	0.18 [12]
GASTROINTESTINAL DISORDERS	0.69 [10]	2.30 [6]	0.73 [7]	0.98 [40]	0.93 [63]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0.69 [10]	2.68 [7]	1.57 [15]	0.54 [22]	0.80 [54]
HEPATOBILIARY DISORDERS	0.41 [6]	0.38 [1]	0.42 [4]	0.25 [10]	0.31 [21]
IMMUNE SYSTEM DISORDERS	0.21 [3]	2.30 [6]	0.52 [5]	0.17 [7]	0.31 [21]
INFECTIONS AND INFESTATIONS	9.28 [135]	14.56 [38]	11.82 [113]	5.47 [223]	7.54 [509]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0.55 [8]	3.07 [8]	0.10 [1]	1.25 [51]	1.01 [68]
INVESTIGATIONS	0.89 [13]	3.45 [9]	0.31 [3]	0.56 [23]	0.71 [48]
METABOLISM AND NUTRITION DISORDERS	0.83 [12]	1.53 [4]	0.52 [5]	0.59 [24]	0.67 [45]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1.38 [20]	6.13 [16]	2.09 [20]	1.10 [45]	1.50 [101]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1.38 [20]	2.68 [7]	1.57 [15]	3.26 [133]	2.59 [175]
NERVOUS SYSTEM DISORDERS	1.44 [21]	5.36 [14]	0.84 [8]	0.74 [30]	1.08 [73]
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0.07 [1]	0.00 [0]	0.73 [7]	0.10 [4]	0.18 [12]
PSYCHIATRIC DISORDERS	0.41 [6]	1.15 [3]	0.42 [4]	0.37 [15]	0.41 [28]
RENAL AND URINARY DISORDERS	0.21 [3]	1.15 [3]	0.21 [2]	0.66 [27]	0.52 [35]
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0.14 [2]	1.15 [3]	0.10 [1]	0.20 [8]	0.21 [14]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1.24 [18]	4.60 [12]	0.52 [5]	0.42 [17]	0.77 [52]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1.31 [19]	6.13 [16]	1.57 [15]	0.66 [27]	1.14 [77]
SOCIAL CIRCUMSTANCES	0.00 [0]	0.00 [0]	0.10 [1]	0.00 [0]	0.01 [1]
SURGICAL AND MEDICAL PROCEDURES	0.28 [4]	0.38 [1]	0.21 [2]	0.37 [15]	0.33 [22]
VASCULAR DISORDERS	0.48 [7]	0.77 [2]	0.94 [9]	0.47 [19]	0.55 [37]

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab. 'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab). 'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".
The incidence of adverse events is reported as rate of adverse events per 100 patient-years.
Patient-years is defined as the number of years the patients exposed to the cohort defining biologic.
(Patient-years = number of days of exposure / 365.25).

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Serious Adverse Events

Table 14 reflects the cumulative incidence of SAEs by system organ class per 100 pt-yrs. The SAE profile in the incident cohort analyses was generally similar to that in the overall cohort analyses. The rate of overall SAEs across all treatment groups was 7.08 per 100 pt-yrs in the incident cohort analyses and 7.18 per 100 pt-yrs across treatment groups in the overall cohort analyses.

The rates of overall SAEs were comparable between the STELARA Incident Cohort (6.72 per 100 pt-yrs) and the Other Non-Sponsor Biologic Incident Cohort (7.45 per 100 pt-yrs, Table 14). The overall rate of SAEs was higher for the Other Sponsor Biologic Incident Cohort (12.68 per 100 pt-yrs) and

was 6.74 per 100 pt-yrs for the No Biologic Group. These SAE rates generally reflect those observed for each treatment group in the overall cohort analyses (STELARA: 5.38 per 100 pt-yrs; Other Non-Sponsor Biologic: 7.37 per 100 pt-yrs; Other Sponsor Biologic: 10.43 per 100 pt-yrs; no biologic: 6.59 per 100 pt-yrs). The SAE rate was lower in the Stelara cohort compared with the other biologics cohorts and similar to the non-biologics cohort.

Table 14: Cumulative incidence rates of serious adverse events per 100 patient-years by system organ class (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1666 Pt-Yrs)	Other Sponsor biologic (N=284 Pt-Yrs)	Other Non-Sponsor biologic (N=993 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=7022 Pt-Yrs)
All events	6.72 [112]	12.68 [36]	7.45 [74]	6.74 [275]	7.08 [497]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0.12 [2]	0.35 [1]	0.20 [2]	0.10 [4]	0.13 [9]
CARDIAC DISORDERS	0.90 [15]	2.46 [7]	1.11 [11]	1.01 [41]	1.05 [74]
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0.12 [2]	0.00 [0]	0.00 [0]	0.02 [1]	0.04 [3]
EYE DISORDERS	0.12 [2]	0.00 [0]	0.10 [1]	0.02 [1]	0.06 [4]
GASTROINTESTINAL DISORDERS	0.30 [5]	0.35 [1]	0.30 [3]	0.39 [16]	0.36 [25]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0.24 [4]	0.35 [1]	0.20 [2]	0.29 [12]	0.27 [19]
HEPATOBILIARY DISORDERS	0.24 [4]	0.00 [0]	0.10 [1]	0.15 [6]	0.16 [11]
IMMUNE SYSTEM DISORDERS	0.06 [1]	1.41 [4]	0.00 [0]	0.00 [0]	0.07 [5]
INFECTIONS AND INFESTATIONS	1.26 [21]	2.11 [6]	1.51 [15]	1.03 [42]	1.20 [84]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0.18 [3]	0.35 [1]	0.10 [1]	0.54 [22]	0.38 [27]
INVESTIGATIONS	0.12 [2]	0.00 [0]	0.00 [0]	0.05 [2]	0.06 [4]
METABOLISM AND NUTRITION DISORDERS	0.06 [1]	0.00 [0]	0.10 [1]	0.15 [6]	0.11 [8]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0.36 [6]	1.06 [3]	0.91 [9]	0.37 [15]	0.47 [33]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0.24 [4]	1.76 [5]	0.50 [5]	0.71 [29]	0.61 [43]
NERVOUS SYSTEM DISORDERS	0.54 [9]	0.70 [2]	0.50 [5]	0.44 [18]	0.48 [34]
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0.12 [2]	0.00 [0]	0.70 [7]	0.07 [3]	0.17 [12]
PSYCHIATRIC DISORDERS	0.24 [4]	0.00 [0]	0.20 [2]	0.12 [5]	0.16 [11]
RENAL AND URINARY DISORDERS	0.18 [3]	0.35 [1]	0.20 [2]	0.34 [14]	0.28 [20]
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0.06 [1]	0.35 [1]	0.00 [0]	0.07 [3]	0.07 [5]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0.36 [6]	0.70 [2]	0.10 [1]	0.27 [11]	0.28 [20]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0.48 [8]	0.35 [1]	0.00 [0]	0.10 [4]	0.19 [13]
SOCIAL CIRCUMSTANCES	0.00 [0]	0.00 [0]	0.10 [1]	0.00 [0]	0.01 [1]
SURGICAL AND MEDICAL PROCEDURES	0.06 [1]	0.00 [0]	0.00 [0]	0.25 [10]	0.16 [11]
VASCULAR DISORDERS	0.30 [5]	0.00 [0]	0.50 [5]	0.25 [10]	0.28 [20]

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".
The incidence of adverse events is reported as rate of adverse events per 100 patient-years.
Patient-years is defined as the number of years the patients exposed to the cohort defining biologic.
(Patient-years = number of days of exposure / 365.25).

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In the incident cohort analyses, the cumulative incidence rates for SAEs per 100 pt-yrs using a 91-day at risk window were similar to those observed based on any prior exposure (Table 15).

Table 15: Cumulative incidence rates of serious adverse events within 91 days of biologic administration per 100 patient-years by system organ class (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454 Pt-Yrs)	Other Sponsor biologic (N=261 Pt-Yrs)	Other Non-Sponsor biologic (N=956 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=6750 Pt-Yrs)
All events	6.19 [90]	13.79 [36]	7.53 [72]	6.74 [275]	7.01 [473]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0.14 [2]	0.38 [1]	0.10 [1]	0.10 [4]	0.12 [8]
CARDIAC DISORDERS	0.83 [12]	2.68 [7]	1.15 [11]	1.01 [41]	1.05 [71]
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0.14 [2]	0.00 [0]	0.00 [0]	0.02 [1]	0.04 [3]
EYE DISORDERS	0.14 [2]	0.00 [0]	0.10 [1]	0.02 [1]	0.06 [4]
GASTROINTESTINAL DISORDERS	0.34 [5]	0.38 [1]	0.21 [2]	0.39 [16]	0.36 [24]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0.21 [3]	0.38 [1]	0.21 [2]	0.29 [12]	0.27 [18]
HEPATOBILIARY DISORDERS	0.21 [3]	0.00 [0]	0.10 [1]	0.15 [6]	0.15 [10]
IMMUNE SYSTEM DISORDERS	0.07 [1]	1.53 [4]	0.00 [0]	0.00 [0]	0.07 [5]
INFECTIONS AND INFESTATIONS	1.17 [17]	2.30 [6]	1.46 [14]	1.03 [42]	1.17 [79]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0.07 [1]	0.38 [1]	0.10 [1]	0.54 [22]	0.37 [25]
INVESTIGATIONS	0.14 [2]	0.00 [0]	0.00 [0]	0.05 [2]	0.06 [4]
METABOLISM AND NUTRITION DISORDERS	0.07 [1]	0.00 [0]	0.10 [1]	0.15 [6]	0.12 [8]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0.34 [5]	1.15 [3]	0.94 [9]	0.37 [15]	0.47 [32]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0.21 [3]	1.92 [5]	0.52 [5]	0.71 [29]	0.62 [42]
NERVOUS SYSTEM DISORDERS	0.48 [7]	0.77 [2]	0.52 [5]	0.44 [18]	0.47 [32]
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0.07 [1]	0.00 [0]	0.73 [7]	0.07 [3]	0.16 [11]
PSYCHIATRIC DISORDERS	0.21 [3]	0.00 [0]	0.21 [2]	0.12 [5]	0.15 [10]
RENAL AND URINARY DISORDERS	0.07 [1]	0.38 [1]	0.21 [2]	0.34 [14]	0.27 [18]
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0.07 [1]	0.38 [1]	0.00 [0]	0.07 [3]	0.07 [5]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0.41 [6]	0.77 [2]	0.10 [1]	0.27 [11]	0.30 [20]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0.41 [6]	0.38 [1]	0.10 [1]	0.10 [4]	0.18 [12]
SOCIAL CIRCUMSTANCES	0.00 [0]	0.00 [0]	0.10 [1]	0.00 [0]	0.01 [1]
SURGICAL AND MEDICAL PROCEDURES	0.07 [1]	0.00 [0]	0.00 [0]	0.25 [10]	0.16 [11]
VASCULAR DISORDERS	0.28 [4]	0.00 [0]	0.52 [5]	0.25 [10]	0.28 [19]

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab. 'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab). 'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".
The incidence of adverse events is reported as rate of adverse events per 100 patient-years.
Patient-years is defined as the number of years the patients exposed to the cohort defining biologic. (Patient-years = number of days of exposure / 365.25).

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Adverse Events of Special Interest

All Adverse Events of Special Interest

In the design of the PSOLAR study, AEs of special interest were pre-specified in the protocol as AEs that, in the opinion of the investigator, do not necessarily meet the regulatory definition and reporting requirements for SAEs but are events of interest to the Sponsor and/or regulatory authorities. These events include the following: malignancies; tuberculosis; opportunistic infections; depression;

hypersensitivity reactions including anaphylactic reactions; autoimmune disease; neurologic or demyelinating events (e.g., progressive multifocal leukoencephalopathy; peripheral demyelination; posterior reversible encephalopathy syndrome [reversible posterior leukoencephalopathy syndrome]); congestive heart failure; hepatotoxicity; hematologic events (e.g., pancytopenia, aplastic anemia, or agranulocytosis); unexpected reaction to a vaccine (e.g., active infection by live attenuated vaccine); cerebrovascular accident; transient ischemic attack; confirmed myocardial infarction; and acquired immunodeficiency syndrome.

AEs of special interest include the following events that were aggregated for clinical clarity and were analysed using Cox proportional hazards regression methodology:

- Malignancy
- Serious infections and infestations
- Major adverse cardiovascular events, including death, non-fatal cerebrovascular accident, and non-fatal myocardial infarction
- All-cause mortality, differentiated by cardiovascular illness and other illness

Given the limited number of pt-yrs of exposure for the Other Sponsor Biologic Incident Cohort, caution should be used in interpreting the results of the Cox proportional hazards regression analyses presented below.

Table 16 provides a summary of AEs of special interest with rates displayed per 100 pt-yrs for treatment groups in the incident cohort analyses. The rates of all-cause mortality, MACE, malignancy excluding NMSC, and serious infections and infestations across all treatment groups in the incident cohort analyses (0.47, 0.53, 0.64, and 1.2 respectively) were generally similar to those observed for each treatment group in the overall cohort analyses (0.43, 0.36, 0.68, and 1.44, respectively).

The rates of all-cause mortality were comparable between the STELARA Incident Cohort (0.12 per 100 pt-yrs) and the Other Non-Sponsor Biologic Incident Cohort (0.10 per 100 pt-yrs, Table 16). The rate of all-cause mortality was 0.00 per 100 pt-yrs in the Other Sponsor Biologic Incident Cohort and was highest for the No Biologic Group (0.74 per 100 pt-yrs). Of note, rates of all-cause mortality were lower for the biologic cohorts in the incident cohort analyses compared with the overall cohort analyses (STELARA: 0.38 per 100 pt-yrs; Other Non-Sponsor Biologic: 0.36 per 100 pt-yrs, Other Sponsor Biologic: 0.38 per 100 pt-yrs). The rates of all-cause mortality for the No Biologic Group were comparable for both the incident cohort (0.74 per 100 pt-yrs) and the overall cohort (0.69 per 100 pt-yrs) analyses.

The rate of MACE was lower for the STELARA Incident Cohort (0.18 per 100 pt-yrs) than for the Other Non-Sponsor Biologic Incident Cohort (0.81 per 100 pt-yrs, Table 16). Rates of MACE for the Other Sponsor Biologic Incident Cohort (0.7 per 100 pt-yrs) and the No Biologic Group (0.59 per 100 pt-yrs) were also higher than for the STELARA Incident Cohort. In contrast, rates of MACE in the overall cohort analyses among the biologic cohorts (STELARA: 0.28 per 100 pt-yrs, Other Non-Sponsor Biologic: 0.34 per 100 pt-yrs, Other Sponsor Biologic: 0.32 per 100 pt-yrs) were generally comparable and lower compared with the rate for the No Biologic Group (0.55 per 100 pt-yrs).

Similarly, the rate of malignancies (excluding NMSC) was lower for the STELARA Incident Cohort (0.12 per 100 pt-yrs) than for the Other Non-Sponsor Biologic Incident Cohort (0.60 per 100 pt-yrs, Table 16). The rate of malignancies for the STELARA Incident Cohort was also lower than those for the Other Sponsor Biologic Incident Cohort (1.41 per 100 pt-yrs) and the No Biologic Group (0.81 per 100 pt-yrs). The STELARA Cohort also had the lowest rate of malignancies in the overall cohort analyses (0.53 per 100 pt-yrs), while the rates of malignancies for the Non-Sponsor Biologic Cohort (0.68 per 100 pt-yrs) and Other Sponsor Biologic Cohort (0.70 per 100 pt-yrs) were similar and

somewhat lower than the rate for the No Biologic Group (0.83 per 100 pt-yrs).

Table 16: Cumulative incidence rates of adverse events of special interest per 100 patient-years (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1666 Pt-Yrs)	Other Sponsor biologic (N=284 Pt-Yrs)	Other Non-Sponsor biologic (N=993 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=7022 Pt-Yrs)
All-cause mortality	0.12 [2]	0.00 [0]	0.1 [1]	0.74 [30]	0.47 [33]
Cardiovascular	0.00 [0]	0.00 [0]	0.00 [0]	0.25 [10]	0.14 [10]
Other	0.12 [2]	0.00 [0]	0.00 [0]	0.32 [13]	0.21 [15]
Unexplained death	0.00 [0]	0.00 [0]	0.1 [1]	0.17 [7]	0.11 [8]
Major adverse cardiovascular events	0.18 [3]	0.7 [2]	0.81 [8]	0.59 [24]	0.53 [37]
Cardiovascular death	0.00 [0]	0.00 [0]	0.00 [0]	0.25 [10]	0.14 [10]
Non-fatal cerebrovascular accident	0.06 [1]	0.00 [0]	0.2 [2]	0.12 [5]	0.11 [8]
Non-fatal myocardial infarction	0.12 [2]	0.7 [2]	0.6 [6]	0.25 [10]	0.28 [20]
Malignancy excluding non-melanoma skin cancers	0.12 [2]	1.41 [4]	0.6 [6]	0.81 [33]	0.64 [45]
Serious infections and infestations	1.26 [21]	2.11 [6]	1.51 [15]	1.03 [42]	1.2 [84]

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".
The incidence of adverse events is reported as rate of adverse events per 100 patient-years.
Patient-years is defined as the number of years the patients exposed to the cohort defining biologic.
(Patient-years = number of days of exposure / 365.25).
Classification of mortality as cardiovascular was determined by the sponsor after reviewing patient narratives and available data.
Classification of malignancy was determined by the sponsor based upon the preferred term and body system classification of individual event terms.

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The Stelara cohort has comparable overall mortality to the non-sponsor biologics cohort. Of note, there was a small data set for "other sponsor biologics cohort" and lower overall mortality as compared with the non-biologics cohort. MACE was lowest in the Stelara cohort.

Additionally, the rate of serious infections and infestations, based on a 91-day exposure window (see Table 17), for the STELARA Incident Cohort (1.17 per 100 pt-yrs) was lower than those for the Other Non-Sponsor Biologic Incident Cohort (1.46 per 100 pt-yrs). The rate for the Other Sponsor Biologic Incident Cohort (2.30 per 100 pt-yrs) was higher than the rate for the STELARA Incident Cohort while the rate for the No Biologic Group (1.03 per 100 pt-yrs) was comparable with that for the STELARA Incident Cohort. A similar pattern for rates of serious infections and infestations was observed in the overall cohort analyses, also based on a 91-day exposure window (STELARA Cohort: 0.89 per 100 pt-yrs, Other Non-Sponsor Biologic Cohort: 1.71 per 100 pt-yrs; Other Sponsor Biologic Cohort: 2.86 per 100 pt-yrs; No Biologic Group: 1.16 per 100 pt-yrs). These rates generally reflect those for serious infections and infestations based on the ever-exposed to treatment definition of exposure listed in Table 16.

In the incident cohort analyses, the cumulative incidence rates for AEs of special interest per 100 pt-yrs using the 91-day at risk window were generally similar to those observed for any prior exposure (Table 17).

Table 17: Cumulative incidence rates of adverse events of special interest within 91 days of biologic administration per 100 patient-years (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1454 Pt-Yrs)	Other Sponsor biologic (N=261 Pt-Yrs)	Other Non-Sponsor biologic (N=956 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=6750 Pt-Yrs)
All-cause mortality	0.14 [2]	0.00 [0]	0.10 [1]	0.74 [30]	0.49 [33]
Cardiovascular	0.00 [0]	0.00 [0]	0.00 [0]	0.25 [10]	0.15 [10]
Other	0.14 [2]	0.00 [0]	0.00 [0]	0.32 [13]	0.22 [15]
Unexplained death	0.00 [0]	0.00 [0]	0.10 [1]	0.17 [7]	0.12 [8]
Major adverse cardiovascular events	0.21 [3]	0.77 [2]	0.84 [8]	0.59 [24]	0.55 [37]
Cardiovascular death	0.00 [0]	0.00 [0]	0.00 [0]	0.25 [10]	0.15 [10]
Non-fatal cerebrovascular accident	0.07 [1]	0.00 [0]	0.21 [2]	0.12 [5]	0.12 [8]
Non-fatal myocardial infarction	0.14 [2]	0.77 [2]	0.63 [6]	0.25 [10]	0.30 [20]
Malignancy excluding non-melanoma skin cancers	0.14 [2]	1.53 [4]	0.63 [6]	0.81 [33]	0.67 [45]
Serious infections and infestations	1.17 [17]	2.30 [6]	1.46 [14]	1.03 [42]	1.17 [79]

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab. 'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab). 'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".
The incidence of adverse events of special interest is reported as rate of adverse events of special interest per 100 patient-years.
Patient-years is defined as the number of years the patients exposed to the cohort defining biologic. (Patient-years = number of days of exposure / 365.25).
Classification of mortality as cardiovascular was determined by the sponsor after reviewing patient narratives and available data.
Classification of malignancy was determined by the sponsor based upon the preferred term and body system classification of individual event terms,

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Benign and Malignant Neoplasms

Table 18 provides a summary of the cumulative incidence of neoplasms by type and preferred term with rates per 100 pt-yrs. Classification of malignancy events was determined by the Sponsor based upon the preferred term and system organ class of individual event terms. Therefore, data for preferred terms listed, may belong to system organ classes other than Neoplasms benign, malignant and unspecified (including cysts and polyps). Malignancies are events of special interest and are collected proactively. The rate of aggregate neoplasms was lowest for the STELARA Incident Cohort and a comparable finding was observed in the overall cohort analyses. Similarly, the rate of malignancies (excluding NMSC) was lowest for the STELARA Cohort in both the incident and overall cohort analyses.

Table 18: Cumulative incidence rates of neoplasms adverse events per 100 patient-years (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1666 Pt-Yrs)	Other Sponsor biologic (N=284 Pt-Yrs)	Other Non-Sponsor biologic (N=993 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=7022 Pt-Yrs)
All events	1.26 [21]	3.52 [10]	1.51 [15]	3.41 [139]	2.63 [185]
Benign	0.54 [9]	1.06 [3]	0.30 [3]	0.42 [17]	0.46 [32]
Acanthoma	0.06 [1]	0.00 [0]	0.10 [1]	0.02 [1]	0.04 [3]
Anogenital warts	0.12 [2]	0.00 [0]	0.10 [1]	0.02 [1]	0.06 [4]
Benign breast neoplasm	0.06 [1]	0.00 [0]	0.00 [0]	0.00 [0]	0.01 [1]
Benign lung neoplasm	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Benign neoplasm of thyroid gland	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Benign ovarian tumour	0.00 [0]	0.35 [1]	0.00 [0]	0.00 [0]	0.01 [1]
Benign prostatic hyperplasia	0.00 [0]	0.00 [0]	0.00 [0]	0.05 [2]	0.03 [2]
Carcinoid tumour pulmonary	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Cardiac valve fibroelastoma	0.06 [1]	0.00 [0]	0.00 [0]	0.00 [0]	0.01 [1]
Colonic polyp	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Keratoacanthoma	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Melanocytic naevus	0.00 [0]	0.00 [0]	0.10 [1]	0.00 [0]	0.01 [1]
Meningioma	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Ovarian adenoma	0.06 [1]	0.00 [0]	0.00 [0]	0.00 [0]	0.01 [1]
Ovarian cyst	0.00 [0]	0.35 [1]	0.00 [0]	0.00 [0]	0.01 [1]
Parathyroid tumour benign	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Pituitary tumour benign	0.00 [0]	0.35 [1]	0.00 [0]	0.00 [0]	0.01 [1]
Pulmonary mass	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Seborrhoeic keratosis	0.06 [1]	0.00 [0]	0.00 [0]	0.00 [0]	0.01 [1]
Skin papilloma	0.12 [2]	0.00 [0]	0.00 [0]	0.05 [2]	0.06 [4]
Uterine leiomyoma	0.00 [0]	0.00 [0]	0.00 [0]	0.05 [2]	0.03 [2]
Vulval neoplasm	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Malignancy excluding non-melanoma skin cancers	0.12 [2]	1.41 [4]	0.60 [6]	0.81 [33]	0.64 [45]
Breast cancer	0.00 [0]	0.00 [0]	0.10 [1]	0.07 [3]	0.06 [4]
Breast cancer recurrent	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Colon cancer	0.00 [0]	0.00 [0]	0.10 [1]	0.00 [0]	0.01 [1]
Colon neoplasm	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Endometrial cancer	0.00 [0]	0.00 [0]	0.10 [1]	0.02 [1]	0.03 [2]
Gastric cancer	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Head and neck cancer	0.00 [0]	0.00 [0]	0.00 [0]	0.05 [2]	0.03 [2]
Hepatic neoplasm malignant	0.00 [0]	0.35 [1]	0.00 [0]	0.00 [0]	0.01 [1]
Liposarcoma	0.00 [0]	0.00 [0]	0.10 [1]	0.00 [0]	0.01 [1]
Lung neoplasm	0.00 [0]	0.35 [1]	0.00 [0]	0.00 [0]	0.01 [1]
Lung neoplasm malignant	0.00 [0]	0.00 [0]	0.00 [0]	0.12 [5]	0.07 [5]
Lymphoma	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Malignant melanoma	0.06 [1]	0.35 [1]	0.00 [0]	0.02 [1]	0.04 [3]
Malignant melanoma in situ	0.00 [0]	0.00 [0]	0.00 [0]	0.10 [4]	0.06 [4]
Mastectomy	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Neuroendocrine carcinoma of the skin	0.00 [0]	0.00 [0]	0.10 [1]	0.00 [0]	0.01 [1]
Non-hodgkin's lymphoma	0.00 [0]	0.00 [0]	0.10 [1]	0.00 [0]	0.01 [1]
Paget's disease of the breast	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Prostate cancer	0.00 [0]	0.00 [0]	0.00 [0]	0.15 [6]	0.09 [6]
Small cell carcinoma	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Small cell lung cancer limited stage	0.00 [0]	0.35 [1]	0.00 [0]	0.00 [0]	0.01 [1]
Synovial sarcoma	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Thyroid cancer	0.06 [1]	0.00 [0]	0.00 [0]	0.02 [1]	0.03 [2]
Uterine cancer	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Waldenstrom's					

	Ustekinumab (N=1666 Pt-Yrs)	Other Sponsor biologic (N=284 Pt-Yrs)	Other Non-Sponsor biologic (N=993 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=7022 Pt-Yrs)
Non-Melanoma Skin Cancer	0.60 [10]	1.06 [3]	0.60 [6]	2.18 [89]	1.54 [108]
Basal cell carcinoma	0.30 [5]	0.00 [0]	0.10 [1]	0.76 [31]	0.53 [37]
Bowen's disease	0.00 [0]	0.00 [0]	0.00 [0]	0.05 [2]	0.03 [2]
Skin cancer	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Skin lesion	0.00 [0]	0.70 [2]	0.00 [0]	0.02 [1]	0.04 [3]
Squamous cell carcinoma	0.30 [5]	0.35 [1]	0.50 [5]	1.15 [47]	0.83 [58]
Squamous cell carcinoma of skin	0.00 [0]	0.00 [0]	0.00 [0]	0.17 [7]	0.10 [7]

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab.
'Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab).
'Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".
The incidence of adverse events is reported as rate of adverse events per 100 patient-years.
Patient-years is defined as the number of years the patients exposed to the cohort defining biologic.
(Patient-years = number of days of exposure / 365.25).
Classification of malignancy was determined by the sponsor based upon the preferred term and body system classification of individual event terms.

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Adverse events of special interest were aggregated for clinical clarity and were analysed using Cox proportional hazards regression methodology to identify predictors of time to first malignancy (excluding NMSC) for the incident cohorts. Potential predictors assessed in these analyses included baseline demographic and clinical characteristics, and use of STELARA, other biologics, and immunomodulators (e.g., methotrexate, cyclosporine, mycophenolate, and oral tacrolimus) prior to the event. Use of immunomodulators (during the registry) was treated as a time-varying covariate. To avoid exclusion of data in the analyses, missing values for baseline demographics (age, gender, ethnicity, BMI) and clinical characteristics (duration of disease, diagnosis of psoriatic arthritis, history of immunomodulator use, number of biologic therapies used historically, and PGA) were imputed as mean for continuous factors and median for categorical factors. Baseline continuous variables of age and duration of disease were transformed to age divided by 10 and duration of disease divided by 5 and were labeled as such.

The results of the incident cohort analysis, based on exposure any time after registration, are presented in Table 19. The models showed a statistically significant lower risk of malignancy with use of STELARA compared with no biologic use (hazard ratio [HR] of 0.122, p=0.019). However, this result is difficult to interpret given the relatively short duration of follow up for the STELARA Incident Cohort and the long latency period prior to clinical presentation typically associated with development of malignancies. Use of other biologics (other Sponsor and Non-Sponsor biologics combined) was not a predictor of malignancy compared to no biologic use (HR of 0.964, p=0.937). In the overall cohort analysis, neither use of STELARA nor other biologics was predictive of malignancy.

In addition, the incident cohort analysis (Table 19) demonstrated that:

- Increasing age was a significant predictor of malignancy (36.5% increased risk/10 years of age) (p=0.011)
- Previous history of malignancy was a significant predictor of malignancy (HR=3.254, 95% confidence interval [CI]: 1.575, 6.726, p=0.001)
- Exposure to immunomodulators on registry was a significant predictor of lower risk of malignancy (HR=0.238, 95% CI: 0.080, 0.709, p=0.010)
- History of immunomodulator use was a significant predictor of increased risk of malignancy (HR=2.330, 95% CI: 1.160, 4.681, p=0.017)

Increasing age (65.0% increased risk/10 years of age, p<0.0001) and previous history of malignancy (HR=2.048, 95% CI: 1.238, 3.273, p=0.003) were also significant predictors of malignancy in the overall cohort analysis. While exposure to immunomodulators was not a significant predictor of lower risk of malignancy, non-white ethnicity was a predictor of lower risk of malignancy in the overall cohort analysis (HR=0.453, 95% CI: 0.243, 0.843, p=0.012).

Table 19: Predictors of time to first malignancy excluding non-melanoma skin cancers (using exposure any time after registration) (Study C0168Z03: Incident Cohort)

	Incidence of Malignancy	Adjusted Hazard Ratio (95% CI)	P-Value*
	44 / 4695 (0.9%)		
No Malignancy: age/10 years - mean(std)	4.84 (1.467)	1.000 (Ref.)	
With Malignancy: age/10 years - mean(std)	6.07 (1.215)	1.365 (1.073, 1.737)	0.011
Females	22 / 2249 (1.0%)	1.000 (Ref.)	
Males	22 / 2446 (0.9%)	0.954 (0.519, 1.756)	0.880
Whites	43 / 3902 (1.1%)	1.000 (Ref.)	
Non-whites	1 / 793 (0.1%)	0.198 (0.027, 1.455)	0.112
Underweight / normal, BMI<25	6 / 952 (0.6%)	1.000 (Ref.)	
Overweight/ obesity class I, 25<BMI<35	27 / 2666 (1.0%)	1.516 (0.613, 3.746)	0.368
Obesity class II-III, BMI >= 35	11 / 1077 (1.0%)	1.815 (0.662, 4.976)	0.247
No Malignancy: Duration of disease/5 years - mean(std)	3.08 (2.719)	1.000 (Ref.)	
With Malignancy: Duration of disease/5 years - mean(std)	4.65 (3.705)	1.093 (0.999, 1.195)	0.052
No psoriatic arthritis	31 / 3368 (0.9%)	1.000 (Ref.)	
Psoriatic arthritis	13 / 1327 (1.0%)	1.047 (0.527, 2.080)	0.896
No history of immunomodulator use	27 / 2856 (0.9%)	1.000 (Ref.)	
History of immunomodulator use	17 / 1839 (0.9%)	2.330 (1.160, 4.681)	0.017
History of 0-1 biologics use	41 / 3971 (1.0%)	1.000 (Ref.)	
History of 2+ biologics use	3 / 724 (0.4%)	1.347 (0.235, 7.733)	0.738
No history of malignancy	33 / 4447 (0.7%)	1.000 (Ref.)	
History of malignancy	11 / 248 (4.4%)	3.254 (1.575, 6.726)	0.001
Baseline PGA 0,1	9 / 952 (0.9%)	1.000 (Ref.)	
Baseline PGA 2,3	32 / 3046 (1.1%)	1.611 (0.748, 3.469)	0.223
Baseline PGA 4,5	3 / 697 (0.4%)	1.035 (0.269, 3.983)	0.960
No biologic use during registry	33 / 2249 (1.5%)	1.000 (Ref.)	
Ustekinumab	2 / 1454 (0.1%)	0.122 (0.021, 0.712)	0.019
Other Sponsor biologics	3 / 255 (1.2%)	1.245 (0.242, 6.417)	0.793
Other biologics	6 / 737 (0.8%)	0.964 (0.389, 2.387)	0.937
No immunomodulator use during registry	40 / 3757 (1.1%)	1.000 (Ref.)	
Immunomodulators	4 / 938 (0.4%)	0.238 (0.080, 0.709)	0.010

* p-value from Wald Chi-square test.
Biologics and immunomodulator factors represent time-varying medication use and is defined as any use between enrollment and the event date.
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Key: BMI=body mass index; CI=confidence interval; PGA=Physician's global assessment; std=standard deviation

The rates of NMSC for the STELARA Incident Cohort and the Other Non-Sponsor Biologic Incident Cohort were the same (0.60 per 100 pt-yrs). The rates for these cohorts were lower compared to the rates for the Other Sponsor Biologic Incident Cohort (1.06 per 100 pt-yrs) and the No Biologic Group (2.18 per 100 pt-yrs, Table 18). In the overall cohort analyses the rate of NMSC was lowest for the STELARA cohort (0.73 per 100 pt-yrs) compared with the other biologic cohorts (Other Non-Sponsor Biologic: 1.68 per 100 pt-yrs and Other Sponsor Biologic: 1.43 per 100 pt-yrs) and the No Biologic Group (2.04 per 100 pt-yrs).

In the incident cohort analyses (Table 18), 7 cases of melanoma were reported; of these, one occurred in a patient exposed to STELARA, one occurred in a patient exposed to an other Sponsor biologic, and 5 occurred in patients exposed to non-biologic therapies. In the overall cohort analyses, a total of 15 melanomas were observed. The rate for the No Biologic Group was the highest (n=6, 0.14 per 100 pt-yrs).

The rates for the biologic cohorts were generally comparable, in light of the small numbers of events (STELARA: n=3, 0.06 per 100 pt-yrs; Other Non-Sponsor Biologic: n=3, 0.03 per 100 pt-yrs; Other Sponsor Biologic: n=3, 0.10 per 100 pt-yrs).

Non-Melanoma Skin Cancer and Melanoma Analysis Relative to PUVA Therapy

An additional analysis evaluating the frequency of NMSC in patients exposed to STELARA and/or PUVA was conducted.

In this analysis, the overall PSOLAR population (N=11,900) was divided into four mutually exclusive groups based on ustekinumab and PUVA exposure: patients never exposed to either ustekinumab or

PUVA, patients ever exposed to only ustekinumab but never exposed to PUVA, patients ever exposed to only PUVA but never exposed to ustekinumab, and patients ever exposed to both ustekinumab and PUVA. The proportions of patients who developed NMSC on registry for each group are shown in Table 20. The PUVA only group had the highest incidence of NMSC (3.3% [42/1,269]; 95% CI: 2.3%, 4.3%), which is consistent with the known association between PUVA and NMSC risk. Logistic regression analyses showed that the odds ratio for NMSC in the comparison between the groups exposed only to ustekinumab and only to PUVA, respectively, was 0.323 (95% CI: 0.187, 0.558, p<0.0001), indicating the odds of developing NMSC for patients exposed to ustekinumab only were 32% of those for patients exposed to PUVA only. The analysis also showed that the no ustekinumab and no PUVA group was less likely to develop NMSC compared with the PUVA only group (odds ratio 0.624, 95% CI: 0.424, 0.916, p=0.0161), and that there was no significant difference in NMSC risk between the group exposed to both ustekinumab and PUVA and the PUVA only group (p=0.1765). This analysis was adjusted for baseline covariates (see Table 21) and, as would be anticipated, demonstrated that older age and white race were also associated with an increased risk of NMSC. Although interpretation of this analysis is limited by the lack of accounting for the timing, duration, or number of PUVA treatments, these data support that exposure to ustekinumab does not appear to increase the risk of NMSC relative to PUVA, and suggest that requiring patients to step-through PUVA prior to initiating ustekinumab therapy may ultimately increase their risk of developing NMSC.

The analysis and overall safety data set and database size support the MAH position that a requirement for patients to “step through” both immunosuppressives as well as PUVA before starting Stelara is no longer required.

Table 20: Summary of non-melanoma skin cancer (Study C0168Z03: All subjects)

	No Ustekinumab and No PUVA	Ustekinumab Only	PUVA Only	Ustekinumab and PUVA
Number of Subjects	6839	2976	1269	816
Subjects with NMSC	110 (1.6%)	21 (0.7%)	42 (3.3%)	14 (1.7%)
95% CI	(1.3%,1.9%)	(0.4%,1.0%)	(2.3%,4.3%)	(0.8%,2.6%)

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Key: CI=confidence interval; NMSC=nonmelanoma skin cancer; PUVA=psoralen and ultraviolet A

Table 21: Logistic regression treatment vs. PUVA only (adjusting for baseline covariates)

Variable	DF	Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Odds Ratio Estimate	Lower 95% Confidence Limit for Odds Ratio	Upper 95% Confidence Limit for Odds Ratio
Intercept	1	-7.2502	0.4803	227.8369	<.0001	.	.	.
Age / 10 years	1	0.6615	0.0631	109.9587	<.0001	1.938	1.712	2.193
Males vs Females	1	0.2110	0.1541	1.8743	0.1710	1.235	0.913	1.670
Non-white vs white	1	-1.5032	0.3897	14.8771	0.0001	0.222	0.104	0.477
Overweight/obesity class I vs Underweight/normal	1	-0.2295	0.1928	1.4167	0.2339	0.795	0.545	1.160
Obesity class 2,3 vs Underweight/normal	1	-0.3984	0.2414	2.7237	0.0989	0.671	0.418	1.078
Duration of disease / 5 years	1	0.0381	0.0243	2.4555	0.1171	1.039	0.990	1.090
Psoriatic arthritis vs None	1	-0.0601	0.1600	0.1410	0.7073	0.942	0.688	1.289
History of immunomodulator use vs no use	1	0.1831	0.1605	1.3023	0.2538	1.201	0.877	1.645
History of 2+ biologics vs 0,1	1	-0.0687	0.1799	0.1458	0.7026	0.934	0.656	1.328
History of malignancy vs no history	1	0.3614	0.2339	2.3869	0.1224	1.435	0.907	2.270
PGA 2,3 vs 0,1	1	-0.00060	0.1579	0.0000	0.9970	0.999	0.733	1.362
PGA 4,5 vs 0,1	1	-0.4292	0.3613	1.4114	0.2348	0.651	0.321	1.322
Ustekinumab only vs PUVA only	1	-1.1298	0.2784	16.4694	<.0001	0.323	0.187	0.558
Ustekinumab and PUVA vs PUVA only	1	-0.4344	0.3214	1.8266	0.1765	0.648	0.345	1.216
Neither vs PUVA only	1	-0.4722	0.1963	5.7867	0.0161	0.624	0.424	0.916

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Key: PGA=Physician’s Global Assessment; PUVA=psoralen and ultraviolet A

An analysis similar to that described above for NMSC was conducted to evaluate the frequency of melanoma in patients exposed to STELARA and/or PUVA (summarised in Table 22). The proportions of patients developing melanoma on registry were generally comparable among those exposed to PUVA only (n=3, 0.2%), STELARA only (n=1, <0.1%), both PUVA and STELARA (n=2, 0.2%), or neither PUVA nor STELARA (n=9, 0.1%), although the small numbers of events make it difficult to

interpret these results.

Table 22: Summary of melanoma skin cancer (Study C0168Z03: All subjects)

	No Ustekinumab and No PUVA	Ustekinumab Only	PUVA Only	Ustekinumab and PUVA
Number of Subjects	6839	2976	1269	816
Subjects with Melanoma	9 (0.1%)	1 (< 0.1%)	3 (0.2%)	2 (0.2%)
95% CI	(0.0%,0.2%)	(0.0%,0.1%)	(0.0%,0.5%)	(0.0%,0.6%)

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Key: CI=confidence interval; PUVA=psoralen and ultraviolet A

Other significant events

Table 23 provides a summary of SAEs of special interest representing identified or potential risks described in the risk management plan for Sponsor biologic therapies (Stelara, Remicade, Simponi). These events of special interest included; autoimmune events (i.e., systemic lupus erythematosus [SLE] and lupus-like syndrome), serious depression including suicidality, hypersensitivity, and neurologic events (i.e., demyelinating disorders and posterior reversible encephalopathy syndrome [posterior reversible leukoencephalopathy syndrome]). The findings in the incident cohort analyses are similar to those observed for the overall cohort analyses.

There were no serious events of SLE or lupus-like syndrome reported across all treatment groups to date. The rate of serious depression/suicidality was 0.13 per 100 pt-yrs across treatment groups in the incident cohort analyses (Table 23) and 0.10 per 100 pt-yrs across treatment groups in the overall cohort analyses. The rates of serious depression/suicidality for the STELARA (0.18 per 100 pt-yrs) and the Other Non-Sponsor Biologic (0.20 per 100 pt-yrs) Incident Cohorts were similar. These rates were higher than the rates for the Other Sponsor Biologic Incident Cohort (0.00 per 100 pt-yrs) and the No Biologic Group (0.10 per 100 pt-yrs). In the overall cohort analyses, the rate of serious depression/suicidality in patients exposed to STELARA was generally low (0.17 per 100 pt-yrs) but higher than the rates in patients exposed to other non-Sponsor biologics (0.09 per 100 pt-yrs), other Sponsor biologics (0.06 per 100 pt-yrs), and no biologic therapies (0.09 per 100 pt-yrs).

There were 5 reports of serious hypersensitivity reaction across treatment groups in the incident cohort analyses (Table 23). None of these reports were in patients exposed to STELARA or other non-Sponsor biologics. Four reports (1.41 per 100 pt-yrs) occurred in patients exposed to other Sponsor biologics and 1 (0.2 per 100 pt-yrs) occurred in a patient exposed to a non-biologic therapy. In the overall cohort analyses, the rate of serious hypersensitivity reactions in patients exposed to STELARA (0.02 per 100 pt-yrs) was similar to the rates in the Other Non-Sponsor Biologic Cohort (0.07 per 100 pt-yrs) and the No Biologic Group (0.02 per 100 pt-yrs) and lower than for the Other Sponsor Biologic Cohort (0.38 per 100 pt-yrs).

There was one report of a serious neurologic event across treatment groups in the incident cohort analyses; this was a case of multiple sclerosis relapse in a patient exposed to STELARA. In the overall cohort analyses there were 3 reports of serious neurological events; all occurred in patients exposed to STELARA (the case of multiple sclerosis relapse, one event of Guillain-Barre syndrome and one report of possible posterior reversible encephalopathy syndrome, which did not meet diagnostic criteria upon further medical review).

Additionally, because it is an identified risk in the MAH's risk management plan for STELARA, a search for events of facial palsy was conducted. There were no events of either non-serious or serious facial palsy observed in patients exposed to STELARA.

Table 23: Cumulative incidence rates of other serious adverse events of special interest per 100 patient-years - by preferred term (Study C0168Z03: Incident Cohort)

	Ustekinumab (N=1666 Pt-Yrs)	Other Sponsor biologic (N=284 Pt-Yrs)	Other Non-Sponsor biologic (N=993 Pt-Yrs)	No biologic (N=4079 Pt-Yrs)	All (N=7022 Pt-Yrs)
All events	0.24 [4]	1.41 [4]	0.20 [2]	0.12 [5]	0.21 [15]
Depression/Suicide	0.18 [3]	0.00 [0]	0.20 [2]	0.10 [4]	0.13 [9]
Affect Lability	0.12 [2]	0.00 [0]	0.00 [0]	0.00 [0]	0.03 [2]
Depression	0.06 [1]	0.00 [0]	0.20 [2]	0.07 [3]	0.09 [6]
Suicide Attempt	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Hypersensitivity	0.00 [0]	1.41 [4]	0.00 [0]	0.02 [1]	0.07 [5]
Anaphylactic Reaction	0.00 [0]	0.70 [2]	0.00 [0]	0.00 [0]	0.03 [2]
Dyspnoea	0.00 [0]	0.35 [1]	0.00 [0]	0.00 [0]	0.01 [1]
Infusion Related Reaction	0.00 [0]	0.35 [1]	0.00 [0]	0.00 [0]	0.01 [1]
Shock	0.00 [0]	0.00 [0]	0.00 [0]	0.02 [1]	0.01 [1]
Neurologic	0.06 [1]	0.00 [0]	0.00 [0]	0.00 [0]	0.01 [1]
Multiple Sclerosis Relapse	0.06 [1]	0.00 [0]	0.00 [0]	0.00 [0]	0.01 [1]

Note: The "Ustekinumab" cohort represents patients whose first biologic received on registry was Ustekinumab. '
Other Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was (Infliximab or Golimumab). '
Other Non-Sponsor biologic' refers to the cohort of patients whose first biologic received on registry was an "Other Non-Sponsor biologics".
The incidence of adverse events is reported as rate of adverse events per 100 patient-years.
Patient-years is defined as the number of years the patients exposed to the cohort defining biologic.
(Patient-years = number of days of exposure / 365.25).
Serious adverse events as classified by the investigator are included in this analysis.

New analyses focusing on the incident biologic cohorts, defined as the subsets of patients initiating a cohort-defining biologic during registry participation, are shown to complement previously submitted analyses for the overall treatment cohorts. Assessment of safety outcomes for the STELARA Incident Cohort relative to the Other Non-Sponsor Biologic Incident Cohort and the No Biologic Group, with consideration of the limitations previously discussed, are most relevant in light of the requested change to the STELARA SmPC.

In addition, given that extended PUVA therapy is known to be associated with an increased risk of NMSC and that PUVA treatment is required before initiating STELARA therapy based on the current version of the STELARA SmPC, the MAH has conducted an analysis evaluating the frequency of NMSC in patients exposed to STELARA and/or PUVA in the overall PSOLAR population.

Post-marketing experience

Post-marketing information has been accruing since the first approval of STELARA on 12 December 2008. The estimated cumulative worldwide exposure to STELARA from launch to 30 June 2013 is 200,315 person-years. Biannual PSURs have been generated for STELARA reflecting the assessment of ongoing post-marketing surveillance of targeted safety events, including serious infections, malignancy, and MACE, as well as broad overall safety surveillance. The evaluation of post-marketing data is part of the MAH's comprehensive safety surveillance program, which includes review of data from ongoing clinical studies and registries. PBRER/PSUR 09 which includes post-marketing data collected from 01 January 2013 through 30 June 2013 was completed in August 2013.

A brief summary of the cumulative evaluation of post-marketing data is presented below:

Three identified risks (serious systemic hypersensitivity reactions, facial palsy and pustular psoriasis) and seven potential risks (serious infection, malignancy, MACE, reversible posterior leukoencephalopathy syndrome [RPLS], serious depression including suicidality, erythrodermic psoriasis and exposure during pregnancy) have been recognised as important risks for STELARA. An overview of significant changes to the Company Core Data Sheet was provided with the Renewal application for STELARA. The most relevant important risks for benefit-risk assessment are serious

systemic hypersensitivity reactions, serious infection, malignancy, and MACE, due to the frequency with which they have been reported and their potential to be life threatening. The other important identified and potential safety risks occur infrequently or are generally reversible and/or manageable.

Serious hypersensitivity reactions (including anaphylaxis) were not observed in the clinical studies with STELARA, but rare reports of such events have occurred in the post-marketing setting. There have been no fatalities from hypersensitivity reactions. Accruing post-marketing data with respect to serious infection, malignancy and MACE have not shown any new safety concerns.

2.3.2. Discussion on clinical safety

In light of the requested change to the STELARA SmPC seeking to establish alignment for non-biologic step-through therapy requirements with those for approved TNF-α inhibitors administered by subcutaneous injection (i.e., etanercept and adalimumab), data from the PSOLAR registry were presented to evaluate the safety profile of STELARA relative to other therapies. New analyses focusing on the incident biologic cohorts, defined as the subsets of patients initiating a cohort-defining biologic during registry participation, are shown to complement previously submitted analyses for the overall treatment cohorts.

The incident cohort analyses were conducted to minimise potential biases related to use of therapies prior to enrolment in PSOLAR and to eliminate potential confounding issues for attributing safety events in the context of multiple exposures over time. Nonetheless, the incident cohort analyses presented are subject to several limitations which limit comparative assessments or interpretation of results. The data are subject to patient selection, reporting, and recall biases, as well as other biases associated with retrospective exposure information. In addition, focusing analyses specifically on the incident biologic cohorts may limit the duration of follow up and numbers of events factored into determining rates of events. Furthermore, rates of AEs presented in data tables are not adjusted for differences in demographic or other characteristics among treatment groups that could potentially impact rates of safety events, in turn limiting the ability to make comparative assessments. However, adjustments for potential confounding factors were made in the Cox proportional hazard models evaluating predictors of time to first event for AEs of special interest.

A total of 2,446 patients represented incident users of biologic therapies in PSOLAR and included 1,454 STELARA Incident Cohort patients, 737 Other Non-Sponsor Biologic Incident Cohort patients (97.2% adalimumab- or etanercept-exposed), and 255 Other Sponsor Biologic Incident Cohort patients (86.7% REMICADE-exposed). Given that nearly all patients in the other Non-Sponsor Biologic Incident Cohort are either adalimumab- or etanercept-exposed, safety data for this cohort is considered largely to be representative of these agents. In addition, given the relatively low numbers of patients and pt-yrs of follow up for the Other Sponsor Biologic Incident Cohort, interpretation of findings relative to this cohort may be limited. A total of 2,249 patients were exposed to non-biologic therapies in these analyses.

Certain features of baseline demographics and characteristics among treatment groups in the incident cohort analyses are notable. Although the STELARA Incident Cohort had the lowest median age, it had a higher proportion of obese patients, a higher median BMI, and on average more severe psoriasis at peak disease activity compared with the Other Non-Sponsor Biologic Incident Cohort and the No Biologic Group. Higher proportions of STELARA Incident Cohort patients had received phototherapy, cyclosporine and methotrexate compared to the Other Non-Sponsor Biologic Incident Cohort and the No Biologic Group, and a markedly higher proportion of patients in the STELARA Incident Cohort had received previous biologic therapy compared with patients in the Non-Sponsor Biologic Incident Cohort. Taken together, these differences suggest that patients with more

recalcitrant psoriasis and patients possibly at greater risk for AEs may be more highly represented in the STELARA Incident Cohort.

Safety outcomes for the incident cohort analyses were compared to those for the overall cohort analyses derived from the most recent annual interval PSOLAR report. Generally, outcomes for AEs, SAEs and AEs of special interest were comparable, indicating relative consistency between the incident cohort and overall cohort analyses.

In examining all AEs, the rate of neoplasms (aggregate) in the overall Other Non-Sponsor Biologic Cohort was somewhat higher compared with the rate for the similar incident cohort and rates of cardiac disorders were generally more comparable across treatment groups in the overall cohort analyses than in the incident cohort analyses. Rates of all-cause mortality were lower for the biologic cohorts in the incident cohort analyses compared with the overall cohort analyses. While the rate of MACE was lower for the STELARA Incident Cohort than for the other biologic incident cohorts in the incident cohort analyses, in the overall cohort analyses the rates of MACE among the biologic cohorts were generally comparable. The rate of malignancies was higher in the Other Sponsor Biologic Incident Cohort than in the Other Non-Sponsor Biologic Incident Cohort, however, in the overall cohort analyses the two cohorts had similar rates. While the rate of serious depression/suicidality for patients exposed to STELARA was higher than the rates for patients exposed to other non-Sponsor biologics and other Sponsor biologics in the overall cohort analyses, the rates of serious depression/suicidality were similar for the STELARA and Other Non-Sponsor Biologic Incident Cohorts and lower for the Other Sponsor Biologic Incident cohort.

Moreover, both the incident cohort and overall cohort analyses revealed no new safety signals for STELARA.

Although not modelled for comparative statistical analyses, rates of MACE, malignancies excluding NMSC, and serious infections trend lower for the STELARA Incident Cohort, while rates of all-cause mortality and depression/suicidality were generally comparable between these incident cohorts. No serious hypersensitivity reactions and one neurologic event were observed among these incident cohorts. As previously indicated, these analyses are subject to limitations; in particular, the small numbers of events for many of these AEs of interest may limit interpretation of these data. Nonetheless, these results, in conjunction with those presented in the most recent annual interval PSOLAR report, support that the safety profile for STELARA is comparable to, and in some cases may be better than the safety profile observed for other non-Sponsor biologic and non-biologic agents.

In addition, because step-through treatment with PUVA is required before initiating STELARA therapy based on the STELARA SmPC, and long-term PUVA therapy is associated with a risk of NMSC, an additional analysis was performed to evaluate the frequency of NMSC in patients exposed to STELARA and/or PUVA. The PUVA only group had the highest incidence of NMSC, which is consistent with the known association between PUVA and NMSC risk. The data show that the NMSC rate was lower for patients exposed to STELARA only compared with patients exposed to PUVA only, and logistic regression analyses showed that the risk of NMSC for the STELARA only group was significantly reduced compared to the PUVA only group. Although interpretation of this analysis is limited by the lack of accounting for the timing, duration, or number of PUVA treatments, these data support that exposure to ustekinumab does not appear to increase the risk of NMSC regardless of whether patients had received PUVA or not, and suggest that requiring patients to step-through PUVA prior to initiating ustekinumab therapy may ultimately increase their risk of developing NMSC. No particular pattern in melanoma incidence was observed relative to STELARA and/or PUVA treatment in a similar analysis, although the small number of events makes it difficult to interpret the results.

Lastly, Cox proportional hazards regression analyses were performed to identify potential predictors

of time to first event for select AEs of interest. Findings based on the incident cohort analyses indicate that STELARA exposure was not a significant predictor of mortality, MACE, malignancy or serious infections. Similarly, exposure to other biologics (other Sponsor and non-Sponsor biologics combined) was not found to be a significant predictor of overall mortality, MACE, malignancy, or serious infections. However, in the overall cohort analyses, exposure to other biologics (compared to no biologics) was observed to be a significant independent risk factor for serious infections.

The impact of duration of exposure to ustekinumab on the incidence of overall malignancies, NMSC, and malignancies other than NMSC in the combined group was evaluated by study period; Year 1, Year 2, Year 3, Year 4, and Year 5. Additionally, rates of these events by dose and by time period of exposure were presented in 5-Year Update. Rates of overall malignancies did not appear to increase over time with 1 to 5 years of exposure. For example, in Year 1, malignancies were reported at a rate of 1.34 in the combined group, compared with 0.75 per hundred subject-years of follow-up in Year 5. A similar pattern was observed in separate analyses of NMSC and malignancies other than NMSC and no dose response or increased rate was observed over time.

In general, the unwanted effects of immunosuppresion (medicinal and natural e.g. HIV infection) become more frequent and pronounced with the passage of time so in the analysis of the immunosuppressive effects of Stelara the status of the cohort which has been exposed for four to five years is of particular interest. The analysis which has been carried out by the MAH dilutes that cohort by including patients with six to eighteen months exposure. Further analysis concentrating on the long term patients and the unwanted effects of immunosuppression were carried out by the MAH. These analyses and interpretation were included in the 5-year submission (EMEA/H/C/000958/II/0028) and were used to evaluate rates of events that could potentially be related to immunosuppression (serious infection, and malignancy) with increasing cumulative exposure. In conclusion, the event rates (events/100 patient years) showed no evidence of increasing with time and tend to be lower at five years than at one year.

The incident cohort analyses performed by the MAH are intended to complement the overall cohort analyses presented in the most recent annual interval PSOLAR report. The incident cohort analyses evaluate the AE profile in the period of first biologic exposure on registry, thus minimizing the impact of exposures prior to enrolment and eliminating potential confounding issues for attributing safety events in the context of multiple exposures on registry over time. Assessment of safety outcomes for the STELARA Incident Cohort relative to the Other Non-Sponsor Biologic Incident Cohort and the No Biologic Group, with consideration of the limitations previously discussed, are most relevant in light of the requested change to the STELARA SmPC to achieve alignment with those for adalimumab and etanercept on requirements for non-biologic step-through therapies.

The PSOLAR database is very helpful in evaluating the immunosuppressive effects of Stelara and so far it suggests that they are similar to those of other ‘biologics’. The median follow up is less than two years.

In summary, the incident cohort analyses demonstrated:

- Outcomes for AEs, SAEs and AEs of special interest for the incident cohort analyses were generally comparable to those for the overall cohort analyses, indicating relative consistency between them.
- The rates of all-cause mortality per 100 pt-yrs for incident user patients exposed to STELARA (0.12) and Other Non-Sponsor Biologics (0.1) were generally similar, and lower than the rate for the No Biologic Group (0.74).

- The rate of MACE per 100 pt-yrs for the STELARA Incident Cohort (0.18) was lower than the rates for the Other Non-Sponsor Biologic Incident Cohort (0.81) and the No Biologic Group (0.59).
- The rate of malignancies (excluding NMSC) per 100 pt-yrs for the STELARA Incident Cohort (0.12) was lower than the rates for the Other Non-Sponsor Biologic Incident Cohort (0.6) and the No Biologic Group (0.81).
- The rates of serious infections and infestations per 100 pt-yrs, based on a 91 day window of exposure, for the STELARA Incident Cohort (1.17) and the No Biologic Group (1.03) were comparable and lower than the rate for the Other Non-Sponsor Biologic Incident Cohort (1.46).
- Cox proportional hazards regression analyses showed no statistically significant greater risk of malignancy, major adverse cardiovascular events, serious infection, or mortality for patients exposed to STELARA or other biologics compared to no biologic use in the incident cohort analyses.
- Rates of depression/suicidality per 100 pt-yrs for the STELARA (0.18) and Other Non-Sponsor Biologic (0.20) Incident Cohorts were comparable; and were higher than the rate for the No Biologic Group (0.10).
- There was one serious hypersensitivity reaction (No Biologic Group); and one neurologic event (STELARA Incident Cohort) across treatment groups.

Additional analyses showed that the NMSC rate was lower for patients exposed to STELARA only compared with patients exposed to PUVA only, and logistic regression analyses showed that the risk of NMSC for the STELARA only group was significantly reduced compared to the PUVA only group. No particular pattern in melanoma incidence was observed relative to STELARA and/or PUVA treatment in a similar analysis, although the small numbers of events make it difficult to interpret the results.

2.3.3. Conclusions on clinical safety

When Stelara was initially licensed for plaque psoriasis the CHMP considered that the use of such a new first in class agent that binds to 2 cytokines and that was to be used long-term in a non-life threatening disease, should be restricted to those with moderate to severe psoriasis who had failed to response, had intolerance or a contraindication to other systemic therapies including cyclosporine, methotrexate AND PUVA. This was in contrast to the wording of the indication for anti-TNF agents where the indication states moderate to severe psoriasis who had failed to response, had intolerance or a contraindication to other systemic therapies including cyclosporine, methotrexate or PUVA. The analysis and overall safety dataset and database size provided support the MAH's request to update the wording of the indication to be in line with anti-TNF therapies, such that patients will not have to "step through" multiple therapies as well as PUVA before they can commence on Stelara.

The findings described in the most recent annual interval PSOLAR report, support that the safety profile for Stelara is comparable to that for other non-Sponsor biologic therapy, as well as non-biologic agents. In turn, these findings support the requested change to the Stelara SmPC to achieve alignment with those for TNF-α inhibitors administered by subcutaneous injection.

The MAH will continue providing yearly reports of the PSOLAR Registry at the time of PSUR submission, as reflected in the RMP.

2.3.4. PSUR cycle

The PSUR cycle remains unchanged.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. The next data lock point will be 31 December 2013.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.4. Risk management plan

2.4.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The following safety concerns have been identified:

Table 1: Summary of safety concerns

Important identified risks	Serious systemic hypersensitivity reactions Facial palsy Pustular psoriasis
Important potential risks	Serious infections including mycobacterial and salmonella infections Malignancy Cardiovascular events Serious depression including suicidality RPLS Exposure during pregnancy Erythrodermic psoriasis
Missing information	Use in paediatric patients Use in patients with hepatic impairment Use in patients with renal impairment Use in patients with a history of latent TB or TB Use in patients with concurrent malignancy or a history of malignancy Use after recent vaccination with live bacterial or live viral vaccines Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C) Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy Use in patients with other forms of psoriasis Use in patients who have undergone allergy immunotherapy

The PRAC agreed.

Pharmacovigilance plans

Ongoing and planned studies in the pharmacovigilance development plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
C0168Z03 (PSOLAR) (Category 3)	Primary objective: to evaluate the safety of Stelara in patients with moderate to severe plaque psoriasis (overlapping forms of psoriasis may be included)	• Serious systemic hypersensitivity reactions • Facial palsy • Pustular psoriasis • Serious infections including mycobacterial and salmonella infections • Malignancy • Cardiovascular events • Serious depression including suicidality • RPLS • Erythrodermic psoriasis • Use in patients with hepatic impairment • Use in patients with a history of latent TB or TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C) • Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy • Use in patients with other forms of psoriasis	Ongoing	Final Report 31 Aug 2021

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
CNTO1275PSO4005 (Nordic Database Initiative) (Category 3)	Primary objective: collection and analysis AEs/SAEs of interest in psoriasis patients (any form of psoriasis [ICD 10 L40]) exposed to ustekinumab, relative to the background risk in non-biologic-exposed controls	• Serious systemic hypersensitivity reactions • Facial palsy • Serious infections including mycobacterial and salmonella infections • Malignancy • Cardiovascular events • Serious depression including suicidality • RPLS • Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with a history of latent TB or TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C) • Use in patients with other forms of psoriasis	Ongoing	01 May 2020
CNTO1275PSO4007 (Pregnancy Research Initiative) (Category 3)	Primary objectives: to collect and analyse information pertaining to pregnancy outcomes of women exposed to ustekinumab during pregnancy and health status in the first year of life of infants born to women following prenatal exposure to ustekinumab as compared with controls.	• Exposure during Pregnancy	Ongoing	01 May 2021

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the updated data submitted, was of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks:		
Serious systemic hypersensitivity reactions	Serious systemic hypersensitivity reactions are specifically addressed in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.	In addition to the SmPC, the sponsor has implemented an educational programme that will provide further educational tools on key benefits and important potential and identified risks of ustekinumab.
Facial Palsy	Facial palsy is specifically addressed in the Undesirable Effects (4.8) section of the SmPC.	No additional risk minimisation activities are proposed.
Pustular psoriasis	Pustular psoriasis will be specifically addressed in the Undesirable Effects (4.8) section of the SmPC.	No additional risk minimisation activities are proposed.
Important potential risks:		
Serious infections including mycobacterial and salmonella infections	Serious infections including mycobacterial and salmonella infections are specifically addressed in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.	In addition to the SmPC, the sponsor has implemented an educational programme that will provide further educational tools on key benefits and important potential and identified risks of ustekinumab.
Malignancy	Malignancy is specifically addressed in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC. The Undesirable Effects section indicates that malignancies have been reported as serious adverse reactions.	In addition to the SmPC, the sponsor has implemented an educational programme that will provide further educational tools on key benefits and important potential and identified risks of ustekinumab.

Malignancy	Malignancy is specifically addressed in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC. The Undesirable Effects section indicates that malignancies have been reported as serious adverse reactions.	In addition to the SmPC, the sponsor has implemented an educational programme that will provide further educational tools on key benefits and important potential and identified risks of ustekinumab.
Cardiovascular events	None	No additional risk minimisation activities are proposed.
Serious depression including suicidality	Depression is listed in the Undesirable Effects (4.8) section of the SmPC (Serious depression including suicidality is not specifically mentioned in the SmPC).	No additional risk minimisation activities are proposed.
RPLS	None	No additional risk minimisation activities are proposed.
Exposure during pregnancy	Exposure during pregnancy is addressed in the Fertility, Pregnancy, and Lactation (4.6) section of the SmPC.	No additional risk minimisation activities are proposed.
Erythrodermic psoriasis	None	No additional risk minimisation activities are proposed.
Missing information:		
Use in paediatric patients	The Posology and Method of Administration (4.2) section in the SmPC indicates that safety in patients less than 18 years of age has not yet been established.	No additional risk minimisation activities are proposed.
Use in renal impairment	This safety concern is addressed in the Posology and Method of Administration (4.2) and the Pharmacokinetic Properties (5.0) sections of the SmPC.	No additional risk minimisation activities are proposed.
Use in hepatic impairment	This safety concern is addressed in the Posology and Method of Administration (4.2) and the Pharmacokinetic Properties (5.0) sections of the SmPC.	No additional risk minimisation activities are proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures

Use in patients with a history latent TB or TB	This safety concern is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	No additional risk minimisation activities are proposed.
Use in patients with concurrent malignancy or a history of malignancy	This safety concern is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	No additional risk minimisation activities are proposed.
Use after recent vaccination with live bacterial or live viral vaccines	Use after recent vaccination with live bacterial or live viral vaccines is addressed in the Special Warnings and Precautions for Use (4.4) and the Interaction with Other Medicinal Products and Other Forms of Interaction (4.5) sections of the SmPC.	No additional risk minimisation activities are proposed.
Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C)	This safety concern is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	No additional risk minimisation activities are proposed.
Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy	Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy is addressed in the Special Warnings and Precautions for Use (4.4) and Interaction with Other Medicinal Products and Other Forms of Interaction (4.5) sections of the SmPC.	No additional risk minimisation activities are proposed.
Use in patients with other forms of psoriasis	None	No additional risk minimisation activities are proposed.
Use in patients who have undergone allergy immunotherapy	Use in patients who have undergone allergy immunotherapy is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	No additional risk minimisation activities are proposed.

The PRAC, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indications.

The CHMP endorsed this advice without changes.

2.5. Update of the Product information

As a consequence of this new indication, section 4.1 of the SmPC has been updated to change the psoriasis indication to the following (additions in **bold and underlined**, deletions in ~~strikethrough~~):

Plaque psoriasis

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) ~~and~~**or** PUVA (psoralen and ultraviolet A).

Section 1 of the Package Leaflet has been updated accordingly as follows:

Stelara is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate ~~and~~**or** phototherapy, or where these treatments did not work.

In addition, the date of latest renewal has been included in section 9 of the SmPC.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Psoriasis is a life-long disease affecting 3% of the population with debilitating physical and psychological effects. Ustekinumab is a first-in-class human mAb to the common p40 subunit that binds to and functionally inhibits IL-12 and IL-23, currently authorized the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, MTX and PUVA.

STELARA is a highly effective treatment for adult patients with moderate to severe plaque psoriasis. The benefit of maintenance dosing is sustained over a 5-year period studied. Based on both clinical measurements of skin disease and improvement of health related quality of life, STELARA has been shown to have a positive impact on patients' lives.

Uncertainty in the knowledge about the beneficial effects

When Stelara was initially licensed for plaque psoriasis the CHMP considered that the use of such a new first in class agent that binds to 2 cytokines and that was to be used long-term in a non-life threatening disease, should be restricted to those with moderate to severe psoriasis who had failed to response, had intolerance or a contraindication to other systemic therapies including cyclosporine, methotrexate AND PUVA. This was in contrast to the wording of the indication for anti-TNF agents where the indication states moderate to severe psoriasis who had failed to response, had intolerance or a contraindication to other systemic therapies including cyclosporine, methotrexate or PUVA. The

analysis and overall safety dataset and database size provided by the MAH support the MAH's request to update the wording of the indication to be in line with anti-TNF therapies, such that patients will not have to "step through" multiple therapies as well as PUVA before they can commence on Stelara.

The efficacy of Stelara is already known and no new efficacy data has been submitted with this application which is accepted by the CHMP.

Risks

Unfavourable effects

Since the initial approval of STELARA in the EU, the MAH has submitted longer-term safety data through 4 and 5 years of exposure from the C0743T08 and C0743T09 studies, which showed that the safety profile of STELARA remained favourable and was consistent with the data submitted in the initial MAA. The population in these studies was consistent with the moderate to severe population studied in clinical studies of other biologics and it should be noted that over 80% of the population failed less than 3 systemic therapies. Furthermore, extensive additional STELARA safety data in other indications has demonstrated a consistent safety profile. Data from large well-controlled Phase 2 and 3 studies in PsA and Crohn's disease demonstrated that STELARA is also well-tolerated in subjects receiving concomitant immunosuppression (e.g., MTX, azathioprine, and 6-MP). The Phase 2 studies in Crohn's disease also demonstrated that induction doses up to 6 mg/kg IV appeared to be generally well-tolerated.

A robust pharmacovigilance program has been in place since prior to the initial MAA, and the MAH has completed 9 PSURs to date. Moreover, the CHMP recently recommended renewal of the STELARA EU marketing authorization with unlimited validity (positive CHMP opinion received 25 July 2013), based on review of data on quality, safety and efficacy, including all variations introduced since the marketing authorization was granted. The CHMP concluded by consensus that the risk-benefit balance of STELARA in the treatment of moderate to severe plaque psoriasis remains favourable.

The aggregate safety data available to date also include analyses from the ongoing MAH's sponsored PSOLAR registry, which collects relevant safety information from psoriasis patients receiving STELARA as well as Non-sponsor Biologics (almost all Non-sponsor Cohort patients received etanercept or adalimumab). The PSOLAR analyses, including the incident user cohort analysis, suggest that the safety profile of STELARA is comparable to that observed with anti-TNFα agents, and in some cases, rates of select AEs of interest trend lower than rates observed for the Non-sponsor Biologic cohort. The analysis results on NMSC support that exposure to ustekinumab does not appear to increase risk of NMSC regardless of whether patients had received PUVA or not, and suggest that requiring patients to step through PUVA prior to initiating ustekinumab therapy may ultimately increase their risk of developing NMSC.

Uncertainty in the knowledge about the unfavourable effects

The additional safety analyses provided by the MAH do not indicate an increase of rates of serious infection or malignancies with increasing cumulative exposure up to five years.

Based on the extended safety data and the analysis of cohorts (both overall and incident) from the PSOLAR registry, the equivalent or better safety for Stelara as compared with non-sponsor biologics can be agreed. The increased risk of NMSC with PUVA makes a requirement for pre-treatment with PUVA problematic now that there is a large and satisfactory safety data base available for Stelara. While a restriction at the time of initial licensing was justified in terms of the unknowns for a new in

class therapy to be used long-term in a non-life-threatening and common disease, it can now be considered that Stelara has a favourable safety profile over 5 years and so a change of the indication wording to be in line with the less restrictive wording for anti-TNFs in plaque psoriasis is acceptable and adequately justified by the data.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The efficacy of Stelara is already known. Stelara is a highly effective treatment for adult patients with moderate to severe plaque psoriasis. The benefit of maintenance dosing is sustained over a 5-year period studied. Based on both clinical measurements of skin disease and improvement of health related quality of life, Stelara has been shown to have a positive impact on patients' lives.

Analyses of the impact of duration of exposure to ustekinumab on the rate of serious infections in the combined ustekinumab group showed that rates of serious infections did not increase over time.

Benefit-risk balance

Based on the extended safety data from clinical studies and post-marketing experience, as well as the analysis of cohorts (both overall and incident) from the PSOLAR registry, the safety profile of Stelara as compared with non-sponsor biologics as well as non-biologic agents has been extensively characterised. While a precautionary restriction at the time of the initial marketing authorisation was justified in view of the unknowns for a ‘new in class’ therapy to be used in a long-term setting in a non-life-threatening and common disease, there is now sufficient evidence to conclude that Stelara has a favourable safety profile over 5 years which justifies a change of the indication wording to be in line with the one for anti-TNFs indicated in plaques psoriasis with a similar safety profile.

Overall, the favourable benefit-risk profile of Stelara in the treatment for adult patients with moderate to severe plaque psoriasis is confirmed by substantial additional information from clinical studies, the PSOLAR registry, and an extensive post-marketing experience.

The findings described in this report, in conjunction with those presented in the most recent annual interval PSOLAR report, support that the safety profile for Stelara is comparable to that for other non-Sponsor biologic therapy, as well as non-biologic agents. In turn, these findings support the requested change to the Stelara Product Information to achieve alignment with those for TNF-α inhibitors administered by subcutaneous injection.

Discussion on the Benefit-Risk Balance

The analysis and overall safety data set and database size support the MAH’s position that a requirement for patients to “step through” both immunosuppressives as well as PUVA before starting Stelara is no longer required.

The MAH will continue providing yearly reports of the PSOLAR Registry at the time of PSUR submission (as described in the RMP).

The overall conclusion is that the benefit / risk balance of Stelara in the management of the claimed indication of plaque psoriasis is positive.

4. Recommendations

The application for extension of indication in the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1), is approvable since other concerns have all been resolved.

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/292/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Final Outcome

Based on the review of the submitted data, the CHMP considers the variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A).

Section 1 of the Package Leaflet has been updated accordingly.

In addition, the date of latest renewal has been included in section 9 of the SmPC.

The requested variation proposed amendments to the SmPC and Package Leaflet.