PURPOSE: A Long-Term, Prospective, Observational Cohort Study of the Safety and Effectiveness of Etanercept in the Treatment of Paediatric Psoriasis Patients in a Naturalistic Setting: A Post-Authorisation Safety Study (PASS)

Statistical Analysis Plan

Study Sponsor	PPD Epidemiology Worldwide Safety Strategy Pfizer Inc. 500 Arcola Rd Collegeville, PA 19426 USA
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Document History

Version No.	Author	Date	Change
1.0	PPD	6 JUL2011	New
1.1	PPD	29OCT2012	Revised to reflected changes to the study Case report forms (CRFs)
2.0	PPD	26JUL2013	Incorporated changes to study protocol and CRFs
3.0	PPD	22MAY2014	Added severity of plaque psoriasis to a listing. Made a few minor changes for clarification.
4.0	PPD	25MAY2015	Major updates to Statistical Analysis Plan (SAP) text includes: updated protocol version to version 6 and corresponding effective date and recruitment target. Updated EPI signatory to PPD . Major updates to SAP TL shell: added a column for "Retrospective Patients" for T2, T3, and T4 series. Updated footnote for T2, T5, T6, L6 series. Added an analysis in T3 for cumulative exposure to etanercept in person-year
4.0	PPD	10JUN2015	SAP text update includes: update Pfizer Biostatistician signatory to Ronald Pedersen. SAP TL shell update includes: T2.1 and T4 footnotes
4.0	PPD	17JUN2015	SAP shell update includes: footnotes to T1, T2.1, T2.3 and T2.4.
4.1	PPD	04-06FEB2019	SAP text to include analysis on treatment emergent adverse events as per Pfizer standard list of outputs. SAP shells including: new tables from Pfizer list of outputs, tables/listings renumbering as per Pfizer standards, header/footnotes updates as per Pfizer minimum standards. Alignment of layout shells to IA and original dry run.

			Quintiles name updated as IQVIA and approval list updates as per current assigned staff. CRF version reference update even if no major changes were added impacting on analysis definition
5.0	PPD	12FEB2019	Finalization (all changes accepted)

Signatures / Approvals

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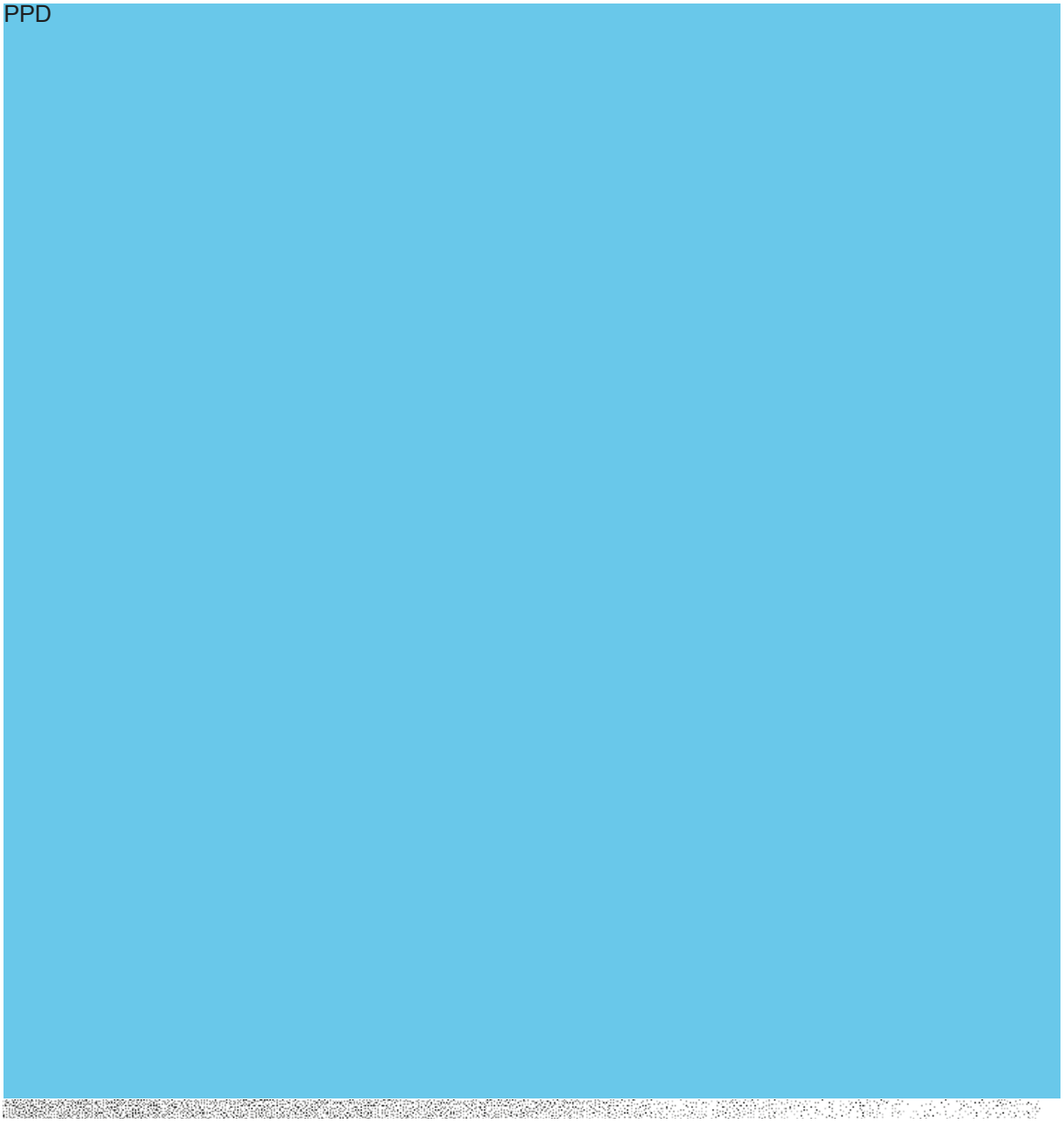
PPD

Abbreviations

ADR	Adverse drug reactions
AE	Adverse Event
ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRF	Case Report Form
ISPE	International Society for Pharmacoepidemiology
MedDRA	Medical Dictionary for Regulatory Activities
NMSC	Non-Melanoma Skin Cancer
PASS	Post-Authorization Safety Study
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SIR	Standardized Incidence Ratio
SOC	System Organ Class
SSC	Scientific Steering Committee
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TNF	Tumor Necrosis Factor

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1. Overview of Study Design

As a consequence of clinical and post-marketing experience across indications, in both adult and paediatric populations and with similar products, current U.S. product labeling for etanercept, a Tumor necrosis Factor (TNF) inhibitor, includes a black box warning addressing the risk of serious infections that may lead to hospitalization or death, including tuberculosis and bacterial sepsis. Due to the mechanism of action, TNF blockade, and the role of TNF in normal immune and inflammatory response function, it is not surprising that the potential for an increased risk for opportunistic and/or serious infections is an ongoing safety concern. In addition, the activity of TNF in preclinical models and potentially in humans raises the possibility that inhibition of this cytokine might potentiate the clinical risk of malignancy; however, clinical data regarding the risk of both lymphomas and solid tumors associated with the use of etanercept and related compounds have been inconsistent. The interpretation of malignancy risk is complicated by the fact that patients treated with etanercept (and other TNF inhibitors) may have an inherent predisposition to malignancy based upon their underlying disease and often receive other medications concomitantly, such as cyclophosphamide, that independently increase the risk of malignancy.

Following a positive recommendation from the Committee for Medicinal Products for Human Use (CHMP) in November 2008, on 22 December 2008 the European Commission extended marketing authorisation of the use of etanercept for treatment of chronic severe plaque psoriasis in children and adolescents (8-17 years of age) who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. In August 2011, Commission approval was received for expansion of the paediatric plaque psoriasis indication to include patients from the age of 6 years. This Registry, a multi-centre, long-term, prospective, observational study, is intended to provide information regarding the long-term safety of etanercept use in paediatric patients with plaque psoriasis, as well as information regarding the use of etanercept in routine clinical practice for the treatment of chronic plaque psoriasis. This Registry constitutes a post-authorization safety study (PASS) and a condition of marketing authorization, to be conducted in compliance with Volume 9a of The Rules Governing Medicinal Products in the European Union (Guidelines on Pharmacovigilance of Medical Products for Human Use). To ensure the quality and integrity of the research, the registry will be conducted under the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology [1].

Note: Italics indicate that they were taken from the original protocol.

Further details regarding the background and rationale of the Registry can be found in the full registry protocol.

2. Purpose of Statistical Analysis Plan (SAP)

The purpose of this SAP is to outline the planned analyses to be completed to support the final study report, interim status and data reports for the purposes of regulatory reporting, and any potential publications. Since this is a long-term registry, this SAP may require updates and adjustments based on the results and evolving thinking or if deemed necessary by the Registry's Scientific Steering Committee (SSC) or the Sponsor following interim data reviews.

The following documents were reviewed in preparation of this SAP:

- Registry Protocol #0881X1-4654 (Pfizer Protocol # B1801035) (Amendment 6, dated 01 July 2014)
- Case report forms (CRFs) (version 7.0, dated 10 January 2017) for this protocol
- International Society for Pharmacoepidemiology (ISPE)'s Guidelines for Good Pharmacoepidemiology Practices (2007)

3. Registry Objectives

The objectives of this Registry are to:

- *Describe the risk of serious and pre-specified opportunistic infection (including tuberculosis) associated with current or recent treatment with etanercept in paediatric plaque psoriasis;*
- *Describe the long-term risk of incident malignancy in paediatric plaque psoriasis patients who have ever received etanercept;*
- *Identify any new, serious potentially unrecognized adverse drug reactions (ADRs) by collecting serious adverse event data in this population; and*
- *Assess effectiveness by describing patterns of treatment with etanercept, including premature discontinuation of etanercept and subsequent treatment with systemic therapies (including re-treatment with etanercept).*

Note: Italics indicate that they were taken from the protocol.

4. Study Population

The Registry is designed for open enrolment of all patients meeting the selection criteria described in the registry protocol, with a recruitment target of 60 to 80 patients in total. The primary inclusion criteria are age ≤ 17 at time of administration of the first dose of etanercept, diagnosis with plaque psoriasis by a dermatologist and a decision made to treat with etanercept prior to enrolment. Patients with a previous history of malignancy, prior treatment with a biologic agent other than etanercept are excluded. The total duration of the registry is approximately 9 years, including 4 years for patient enrolment and 5 additional years to complete follow-up on all enrolled patients.

Any patient who receives at least one dose of etanercept will be included in the evaluation for safety. The primary focus of this Registry is safety; however, to the extent possible effectiveness (or lack of effectiveness) will be inferred from patterns of treatment and re-treatment. In addition, the change of severity of plaque psoriasis as a measure of effectiveness will also be assessed, if these data are available among the majority of patients.

Primary analyses will be limited to prospective data, i.e., events reported during participation in the registry. Serious and pre-specified opportunistic infections and malignancies reported as part of retrospective data collection will be included in a summary of medical history and co-morbid conditions.

5. Variables Used for Analysis

5.1 Data Sources

Data will be collected from treating physicians, who will provide information on current medications and status of the Registry patients at enrolment and at each suggested follow-up assessment.

Following enrolment in the registry, the physician will also provide information by retrieving medical record information at his/her own institution and other health care settings, as appropriate. Data will be collected and recorded directly from the patient or their parent/guardian only if the patient has been lost to follow-up by the physician. If any of the outcomes of interest are reported directly by patients or their parents/guardians, additional attempts to collect supporting information from treating physicians will be made. In order to provide complete narratives for interim and final study reports, for any reported malignancies, any additional information provided via NIS SAE Form AEM01 and other follow-up reports to Pfizer's drug safety department or the Endpoint Adjudication Panel will be used to augment the data collected in the CRF.

Baseline data are expected to be recorded at the time of enrolment to this registry. Follow-up data are to be collected every 3 months (± 4 weeks) during the first 2 years, and every 6 months (± 4 weeks) during Year 3 through Year 5 of participation, either at the time of routine clinical visits, or alternatively via telephone interview.

5.2 Definition and measurement of outcomes of interest

5.2.1 Serious and opportunistic infections

Analyses will include all episodes of serious infection experienced by a single individual.

Serious infections are defined as any infections that:

- Are life-threatening or resulting in disability
- Require intravenous antibiotic treatment

- Require hospitalization

Serious infections are also further classified as nosocomial or not nosocomial/unknown. Serious infections are characterized by the physician's open text report of infection site (i.e., bodily location), open text report of pathogen, date of diagnosis, date of resolution (or ongoing) and most recent dose of etanercept prior to diagnosis. If date of most recent dose is not known, whether the dose was within 28 days prior to diagnosis is requested (refer to Section 5.3.1 for further details regarding establishing exposure at the time of infection diagnoses).

Opportunistic infections of interest include the following protocol-specified infections and pathogens (see table below):

All infections, including the designation as serious, opportunistic or nosocomial, will be reviewed by the Registry's Endpoint Adjudication Panel prior to inclusion in any analyses.

Bacterial	Fungal	Protozoan	Viral
Salmonella bacteraemia	Aspergillus sp. (Aspergillosis)	Cryptosporidiosis	Cytomegalovirus
Campylobacteriosis	Invasive Candida albicans	Isosporiasis	
Shigellosis	Coccidioidomycosis	Microsporidiosis	JC Virus (progressive multifocal leukoencephalopathy)
Mycobacterium tuberculosis	Cryptococcosis		Disseminated or central nervous system herpes zoster
Mycobacterium avium	Histoplasmosis	Acanthamoebiasis	Kaposi's sarcoma (herpesvirus 8)
Mycobacterium kansasii	Blastomycosis	Toxoplasmosis	BK virus
Syphilis/neurosyphilis	Paracoccidioidomycosis	Trypanosomiasis (Chagas disease)	
Pseudomonas aeruginosa	Sporotrichosis	Leishmaniasis	
Acinetobacter baumannii	Penicilliosis		
Listeriosis	Zygomycosis		
Nocardiosis	Pneumocystosis		
Legionellosis			
Actinomycosis			
Bartonellosis			

5.2.2 Malignancies

The following malignancies are reported as part of the Registry:

- Solid malignant tumors
- Non-melanoma skin cancers
- Malignant tumors of hematopoietic and lymphoid tissues
- Carcinomas in-situ

The malignancy type is specified by open text. In order to meet the case definition for malignancy, a pathology report or a physician's notation of specific tumor histology will be required. All malignancies will be evaluated and coded by the Registry's Endpoint Adjudication Panel prior to inclusion in any analyses.

5.2.3 Other adverse events

All other Serious Adverse Events (SAEs) and non-serious Adverse Events (AEs) will be collected and coded using Medical Dictionary for Regulatory Activities (MedDRA). All SAEs will be reviewed by the Endpoint Adjudication Panel prior to inclusion in any analyses.
As part of the data collection for the Registry, physicians are also asked whether pregnancy exposure, lactation exposure, medication error (overdose, or inadvertent or accidental exposure) have occurred. These are to be reported for the purposes of meeting regulatory reporting requirements but are not part of the objectives of the Registry and are not included as part of any analyses.

5.2.4 Treatment emergent adverse events

Treatment emergent adverse events will be defined as events having onset date greater or equal to the first administration of Enbrel reported in the study. All events with missing start date will also be considered as treatment emergent.

5.2.5 Effectiveness

To the extent possible effectiveness (or lack of effectiveness) will be inferred from patterns of treatment and re-treatment. The recommended course of etanercept treatment for paediatric psoriasis is for up to 24 weeks; physicians should consider discontinuation of etanercept if a satisfactory response is not achieved by 12 weeks.

The following data will be used to evaluate effectiveness:

- Whether a patient receives initial course of etanercept for less than 24 weeks and reason for discontinuation is not recorded as "clearing of psoriasis"
- Whether a patient is required subsequent treatment periods of etanercept or other systemic therapies after completion of initial course
- Whether a patient receives subsequent treatment periods of etanercept for less than 24 weeks
- Whether a patient has decreased disease severity after treatment with etanercept compared to baseline

Note: Treatment for individual patients may not follow recommendations included in the product labeling, e.g., treatment with etanercept may be reported as continuous and as longer than 24 weeks initially, rather than being reported as discrete treatment periods. Any deviations from the planned analyses will be described in the interim and/or final study reports, as applicable.

5.3 Definition and measurement of exposure/risk windows

5.3.1 Etanercept

TREATMENT PERIODS (INITIAL AND SUBSEQUENT)

It is anticipated that the etanercept treatment status for each patient will change throughout follow-up. A standard course of etanercept treatment is expected to last up to 24 weeks. Patients successfully responding to the first etanercept treatment course may be exposed to subsequent treatment (i.e., when patients experience a disease flare) and time window between 2 (or more) consecutive courses of treatment may vary substantially.

For the initial course of etanercept, whether the patient completed 24 weeks of treatment is recorded (yes/no), and if no, the number of weeks of treatment will be reported. Completion of initial 24 weeks of etanercept is defined as starting the first dose of etanercept within 30 day before the enrolment date or any time after enrolment date, and continuing for at least 168 days.

For each subsequent treatment period of etanercept, start and stop dates of treatment are collected. For all subsequent periods, the duration of treatment in weeks will be calculated. Cumulative exposure will be calculated by the sum, for each etanercept treatment period, of: [last dose date – first dose date] + 28. If there are less than 28 days between treatment periods, exposure will be considered uninterrupted (i.e., part of the same treatment period).

CURRENT/RECENT TREATMENT VERSUS PAST TREATMENT
In order to interpret reported events, time at risk of occurrence is established based on current or recent (within 28 days) exposure and past exposure.

Past exposure is defined as any exposure to etanercept, at any dose, with no reported exposure within the last 28 days.

Current/recent exposure is defined as on active etanercept treatment at the time of the event, or last dose of treatment within 28 days (inclusive) preceding the event.

5.3.2 Other immunosuppressants and concomitant medications

Treating physicians are asked to report information regarding use of medications, including alternative treatments for psoriasis, or other immunosuppressant and immune-modulator medications, including:

- Type of treatment or medication name
- Status of exposure to medication (i.e., current or past)

- Dose and duration of exposure
- Indication for use

In addition, when an opportunistic or other serious infection is reported, current/recent treatment (i.e., within 28 days) with any immunosuppressant or steroid will be evaluated.

5.4 Definition and measurement of covariates

A critical element of understanding the potential association of adverse outcomes with etanercept product exposure is the inclusion of appropriate covariates in the analyses. In order to better characterize the patients who experience or do not experience the events of interest, the following additional patient characteristics and exposures with the potential to affect clinical outcomes or interpretation of the data are collected at baseline:

Demography:

- Age
- Gender
- Race/ethnicity

Related to plaque psoriasis:

- Duration of disease at baseline
- Severity of plaque psoriasis (none, mild, moderate, severe)
- Diagnosis of psoriatic arthritis
- Previous (or current) use of common plaque psoriasis therapies (topical or systemic)
- Response to previous or current therapies (none, poor, fair, good, excellent/complete, unknown)

Other covariates:

- Medical history and co-morbid conditions
- Other concomitant medications

Current plaque psoriasis disease severity, co-morbidities and all medication exposures are also collected/updated at each follow-up time point.

6. General Considerations for Analysis

6.1 Analysis software and coding

All AE verbatim terms will be recorded and coded using MedDRA.

All computations and generation of tables, listings and data for figures will be performed using Statistical Analysis Software (SAS)® version 9.2 or higher (SAS Institute, Cary, NC, USA).

6.2 Sample size

No formal sample size calculation was performed in the design of the Registry since the goal is to obtain participation by all eligible patients. It should also be noted the study is descriptive only (i.e., non-comparative) and therefore not designed to assess differences amongst etanercept users or users of other therapies. Current available data are insufficient to project population-based estimates of paediatric patients with severe psoriasis treated with conventional systemic therapy who were not well-controlled and would warrant further intervention such as that potentially afforded by etanercept.

The best research estimates suggest that during the first 3 years following market authorization for treatment of severe disease in patients aged 8 through 17, approximately 250 patients will be treated with etanercept throughout Europe. Long-term follow-up studies, with a young and potentially highly mobile population and widely-spaced follow-up timepoints (Years 3 – 5), may incur a higher rate of loss-to-follow-up. The Registry will target 100 to 200 patients.

6.3 Methods for withdrawals, missing data, and outliers

Patients may withdraw consent at any time. If a patient withdraws prior to completing the Registry follow-up period, any reason for withdrawal is to be documented. All information already collected as part of the Registry will be retained for analysis.

Several attempts will be made to contact patients and to limit missing data. In general, there will be no imputation of missing data. Data will be presented and summarized as they were recorded. However, in estimating the person-time at risk for inclusion in the sum of current/recent etanercept use, missing start or stop date of adverse events or etanercept treatment will be handled as follows:

(1) If the day element of the start date of the most recent period of etanercept exposure is missing, it will be assumed to be the 15th of the month.

(2) If the day element of the start date of a serious/pre-specified opportunistic infection or other SAE is missing, it will be assumed to be the 15th of the month.

(3) If the last dose of the most recent period of etanercept exposure prior to onset of a serious/pre-specified opportunistic infection or other SAE is recorded as unknown, the reporter is asked to indicate whether it was known to be within the 28 days prior to event onset. The time at risk will be estimated to be the larger of the following: (a) time between the start date of the most recent period of etanercept exposure prior to the onset of AE and the AE onset date, and (b) 29 or (1 + 28) days.

(4) If the month element of the event or treatment are missing, it will be assumed to be the mid of the year, i.e., July 1st.

The number of missing start or stop date of adverse events or etanercept will be examined, and its impact on analysis will be assessed at the time of analysis. Every effort will be made to query and resolve any missing data. Additional sensitivity analysis may be performed if deemed necessary.

6.4 Populations for analysis

The population for analysis includes all enrolled patients who are documented as having received at least one dose of etanercept. No internal comparator group is included in the Registry; however, where applicable, external data sources such as geographically appropriate (country-specific) population-based incidence rates (age and gender-specific) of malignancy and tuberculosis (TB) may be used to generate standardized incidence ratios (SIRs) to aid interpretation of incidence rates of malignancies and tuberculosis estimated based on data from the registry. Due to the small sample size and expected rarity of the events, this approach may be of limited value.

6.5 Planned subgroups

Descriptive analyses will be stratified, where specified, by:

- Enrollment type: Prospective (i.e., patients who started etanercept within 30 days before the enrollment date or any time after enrollment date) or retrospective
- Treatment period (initial 24 weeks/post 24 weeks/all follow-up)
- Completion of initial 24 weeks of etanercept exposure (yes/no/unknown)

Analysis of outcomes of interest:

- Etanercept exposure status (current/recent or past)
- Infection status (none during follow-up/in association with recent or current exposure/in association with past exposure)

6.6 Derivations

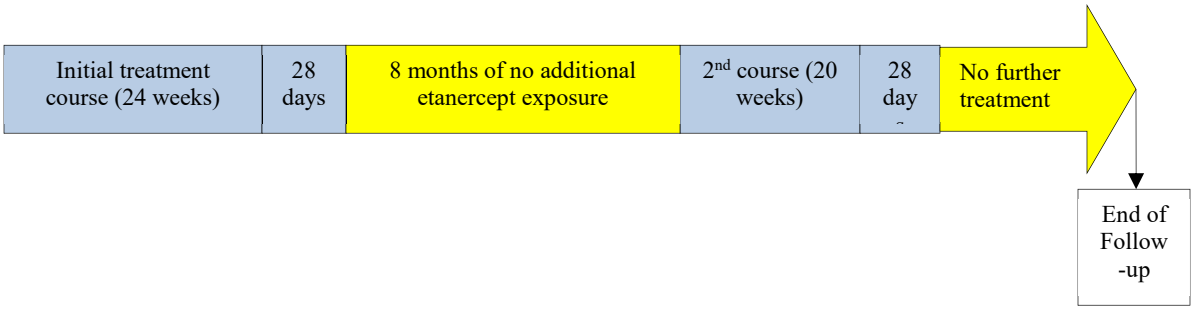
The following derived/calculated values will be used:

- Age at enrollment in years: [date of enrollment – date of birth+1]/365.25
- Duration of disease at enrollment in years: [date of enrollment – date of diagnosis+1]/365.25
- Cumulative exposure in weeks by the duration of chronic exposure for each period of etanercept exposure: [(last dose date – first dose date+1) + 28]/7. A treatment period is defined as continuous treatment with no interruptions of more than 28 days. Restarting treatment within 28 days is considered as having continuous exposure
- Duration of each etanercept treatment period (in weeks): (last dose date – first dose date+1)/7
- Time at risk of malignancy (in years): [date of malignancy diagnosis or end of follow-up if no malignancy is found – initial treatment dose date+1]/365.25

  - The follow-up time for patients who had malignancies will be censored at the diagnosis date for each type of malignancy. The follow-up time after diagnosis of a malignancy will not be included in the calculation of time at risk or not at risk for the same type of malignancy. However, patients who reported a malignancy are still at risk of having a different type of malignancy. Malignancy types include but are not limited to: Solid malignant tumors, Non-melanoma skin cancers, Malignant tumors of hemopoietic and lymphoid tissues, Carcinoma in-situ.

- Time at risk (in years; for the current/recent etanercept-treated group only) of serious or pre-specified opportunistic infection (excluding malignancies) and other SAEs (excluding serious or pre-specified opportunistic infection and malignancies), respectively: cumulative period of etanercept exposure defined as the sum of each etanercept treatment period, [date of last dose – date of first dose +1 + 28]/365.25.
- Time <u>not</u> at risk (this applies to time in years accrued after discontinuation of etanercept while followed in the registry, and excludes malignancies) of serious or pre-specified opportunistic infection and other SAEs, respectively: cumulative period <u>without</u> current/recent use of etanercept {[(date of study discontinuation) – (date of last dose + 28)+1] + [intervals between treatment periods > 28 days]}/365.25. For analysis purposes, time not at risk is the total study follow-up time minus the time at risk, which is defined above.
- Incidence rate is calculated as the number of individual events observed during the time at risk, divided by the total number of patient-years at risk for the event, multiplied by 100. Please note that the time at risk for malignancy will be censored at the diagnosis date of that specific malignancy.

In the example below, all person-time in blue would contribute to the 'current/recent' category, while all person-time in yellow would contribute to the 'past treatment' category for the assessment of SAEs and serious or opportunistic infections. Patients would be considered at risk of malignancies in both the blue and yellow periods.



7. Primary and Secondary Analyses

Evaluations and interpretations will be based on point estimates and 95% confidence intervals (CI) as evaluation of the statistical precision around the point estimate, unless otherwise specified. No formal hypothesis testing is planned. This approach follows the *Guidelines for Good Pharmacoepidemiology Practices*, Section D, point 10 [1]. Unless otherwise specified, all listings and tables are based on the total Registry population at the time of data cut-off for analysis.

7.1 Summary of baseline characteristics and demography

For enrolled patients, line listings for all baseline characteristics (including medical history) and demography data will be generated.
The following tabular summaries will be generated:

- Demography (age at enrollment, gender, race/ethnicity)
- Plaque psoriasis status (duration of disease, baseline severity, presence of psoriatic arthritis, age at diagnosis of plaque psoriasis)
- Previous/current plaque psoriasis therapies (proportion of patients with previous/current use of topical steroids, methotrexate, cyclophosphamide, etc)

Demography summary will also be generated by gender as per basic result disclosure (Pfizer standard).

7.2 Etanercept exposure

In addition to a patient listing of all etanercept exposure, the following tabular summaries will be generated on all enrolled, prospective patients and by completion of initial 24 weeks of etanercept exposure:

- Summary of treatment duration
    - Mean (Standard Deviation (SD)), median and range (in weeks)
    - Proportion receiving ≤ 24 weeks of treatment (initial course)
    - Proportion receiving > 24 weeks of continuous treatment (initial course)

- Summary of patients requiring additional treatment with systemic therapy (etanercept or other non-etanercept therapies)
    - Proportion of patients requiring additional treatment, by subsequent treatment type
- Summary of overall treatment over the entire 5 years of study participation starting from enrollment to the end of follow-up.
    - Duration of exposure to etanercept
    - Cumulative dose of etanercept
    - Total number of treatment periods of etanercept [complete (≥ 24 weeks), incomplete (< 24 weeks) and overall]

7.3 Risk of infection associated with etanercept exposure

The following patient listings will be generated:

- All serious and opportunistic infections
    - Serious (infection site, pathogen, onset date, resolution date or ongoing, date of last etanercept dose prior to infection)
    - Opportunistic (infection type, nosocomial, onset date, resolution date or ongoing, date of last etanercept dose prior to infection)
    - Concomitant therapies (all) within 28 days prior to each infection
    - Immunosuppressant/steroid use within 28 days prior to each infection

In addition, the following tabular summaries will be presented:

- Number of unique patients, total number of events, and incidence rate of all reported serious and opportunistic infections (by MedDRA System Organ Class (SOC) and Preferred Term (PT))
- Overall incidence rate, stratified by exposure type (current/recent and past)
- Overall incidence rate, stratified by treatment period (≤ 24 weeks, > 24 weeks) during any period of etanercept treatment
- Summary of use of other immunosuppressants or steroids within 28 days prior to serious and opportunistic infection
- Summary of baseline characteristics (demographic and clinical characteristics) stratified by infection status (none reported, reported in association with current or recent exposure, reported in association with past exposure, and specifically associated with initial course)
- Summary of number of infections reported per patient (overall and by exposure status)
- If an adequate number (≥5) of infections are recorded in each of the current/recent and past treatment groups, relative risk (95% CI) of infection will be calculated as the

incidence rate ratio (current/recent vs. past treatment with etanercept). The 95% CI was constructed using the formula below.

$$\hat{IRR} = \frac{a}{PT_1} \Big/ \frac{b}{PT_2}$$

$$\hat{IRR}_L = \left(\frac{PT_2}{PT_1}\right)\left(\frac{a}{b+1}\right)\frac{1}{F_{\alpha/2,2(b+1),2a}}$$

$$\hat{IRR}_U = \left(\frac{PT_2}{PT_1}\right)\left(\frac{a+1}{b}\right)F_{\alpha/2,2(a+1),2b}$$

Where a and b are the number of infections during the current/recent and past treatment with etanercept, respectively, and PT_1 and PT_2 are the cumulative patient-year follow-up for the current/recent and past treatment with etanercept, respectively [2].

- If any reports of tuberculosis are identified, standardized incidence ratio (SIR) (95% CI) will be calculated adjusting for age and sex (local population-based rates of tuberculosis will be used).

7.4 Risk of malignancy associated with any etanercept exposure

All malignancies reported will be presented as a listing, including malignancy type (verbatim and MedDRA PT, date of diagnosis and date of resolution (if applicable)), all reported prior drug exposures (up to the time of diagnosis), interval between first etanercept exposure and diagnosis of malignancy, duration of actual exposure (excluding temporary interruptions, if any), and total cumulative exposure.

Risk of incident malignancy in patients who have ever received etanercept will be estimated as number of events over the total time at risk, defined as the time since first dose. If any patients do develop a malignancy during follow-up, incidence rates will be presented and SIR analyses using geographically appropriate population-based norms (age and gender-adjusted) may be used, depending on the data available:

- Incidence rate and SIR (95% CI), for all cancers reported excluding non-melanoma skin cancer and cancer in-situ (primary analysis)

If any patients develop the following specific type of malignancy during follow-up:

- Incidence rate and SIR (95% CI), limited to hematopoietic cancers (secondary analysis)
- Incidence rate of non-melanoma skin cancer (NMSC), and SIR (95% CI) if appropriate population-based rates for NMSC are available (secondary analysis)

- Incidence of cancer in-situ, and SIR (95% CI) if appropriate population-based rates for cancer in-situ are available (secondary analysis)

In addition, narrative summaries for any malignancies reported, based on data captured in the Registry database, additional information provided to the Endpoint Adjudication Panel such as pathology reports and data received from Pfizer drug safety will be included as part of the analysis.

7.5 Other serious adverse events associated with exposure

A patient listing of all SAEs will be generated, including verbatim term and MedDRA SOC and PT, onset date, total cumulative exposure at time of onset, date of last dose of etanercept prior to onset, date of first dose of etanercept and calculated interval between last dose and onset in days [if precision of event dates allow, otherwise use response to question whether within 28 days (yes, no, unknown)].

The following summaries will also be presented:

- Number of unique patients, total number of events, and incidence rate of all reported SAEs (by MedDRA SOC and PT)
    - Including serious and opportunistic infections and excluding malignancies
    - Excluding serious and opportunistic infections and malignancies
    - By treatment period (initial 24 weeks/ post 24 weeks/all follow-up)

Summary of SAE distribution [mean # of events reported per patient (SD), median, range]

Summary of serious TEAE will also be provided as per basic results disclosure (Pfizer standard). The events described will be identified based on serious yes/no variable reported as Yes and onset date greater or equal to the first administration of Enbrel reported in the study. Serious events with missing onset date will be also included.

7.6 Other adverse events associated with exposure

The following Pfizer standard summaries will also be presented:

- Discontinuation due to AE
- TEAE (all causality and related)
- TEAE by severity (all causality and related)
- TEAE by severity and relationship

Summary of both serious and non-serious TEAE (all causality) and summary of non-serious TEAE with frequency ≥ 5% (all causality) will also be provided as per basic results disclosure (Pfizer standard).

A patient listing of all non-serious AEs and all AEs reported as possibly related to etanercept will be generated, including verbatim term and MedDRA SOC and PT, onset date, total cumulative exposure at time of onset, date of last dose of etanercept prior to onset, date of first dose of etanercept and calculated interval between last dose and onset in days [if precision of event dates allows, otherwise use response to question whether within 28 days (yes, no, unknown)]. Summaries of number of unique patients and total number of events of all reported non-serious AEs (by MedDRA SOC and PT) will also be presented.

7.7 Effectiveness of treatment

Treatment discontinuation for lack of desired therapeutic effect will, for purposes of analysis, serve as a proxy for treatment effectiveness.

A listing will be generated presenting all patients discontinuing the initial course of etanercept which will include reason for discontinuation, duration of initial course and use of previous systemic therapies.

The following summaries will also be presented:

- Summary of proportion of patients who discontinue etanercept early (< 24 weeks) due to lack of effect, AE or intolerance (primary analysis) during any period of etanercept treatment
- Summary of treatment discontinuation among all patients during any period of etanercept treatment, by each reason and in aggregate (primary analysis)
- Summary of baseline characteristics, stratified by completion/non-completion of initial 24 weeks of therapy (primary analysis)
- Summary of proportion of patients who discontinue at > 24 weeks during any period of etanercept treatment due to lack of effect, AE or intolerance (secondary analysis)
- Summary of proportion of patients who have decreased disease severity after treatment with etanercept during any period of etanercept treatment compared to baseline (as a secondary analysis) stratified by completion of initial 24 weeks.

8. Other Analyses

Additional exploratory analyses may be performed, depending on the availability of data, including replication of certain analyses stratified by level of cumulative exposure.

9. Reporting

9.1 Enrollment and progress

The number and percentage of patients enrolled and patients discontinued from the Registry will be summarized annually. Also, early identification of potential demographic and clinical differences between patients that enroll in the Registry and those who choose not to enroll (to the

extent feasible based on the enrollment log), or cannot be contacted, will be attempted, in order to better understand the representativeness of the enrolled population, and therefore evaluate the generalizability of the study results.

9.2 Annual reporting

Annual reports will be generated starting one year after start of enrollment. These reports will include, but are not limited to:

- Total number of patients enrolled
- Summary of demographic and baseline disease characteristics (Section 7.1)
- Summary [median, mean (SD) and range] of patient follow-up time in the Registry
- Limited analyses of the outcomes of interest, dependent on the quantity of data available, as described in Sections 7.1 through 7.6 of this document.

9.3 Final study report

A final registry report will be prepared at closure of the Registry database, when all data collection procedures are completed. The final report will encompass all planned analyses described in this SAP.

10. References

[1] International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP), revision 2. April 2007. Available at http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Last accessed January 2009.

[2] Sahai H, Kurshid A. *Statistics in epidemiology: methods techniques and applications*. CRC Press 1996. Technical validation is available at http://www.statsdirect.com/help/. Last accessed November 2010.

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