NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

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)

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[redacted]

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
CHMP	Committee for Medicinal Products for Human Use
CRF	case report form
DMARDs	disease-modifying anti-rheumatic drugs
DSU	Drug Safety Unit
EC	Endpoint Committee
EDC	electronic data capture
EIU	exposure in-utero
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
ICF	informed consent form
ICH	International Committee on Harmonisation
IEC	independent ethics committee
ISPE	International Society for Pharmacoepidemiology
JC virus	John Cunningham virus
JIA	juvenile idiopathic arthritis
MedDRA	Medical Dictionary for Regulatory Activities
NICE	National Institute for Health and Clinical Excellence
NRP	national responsible person
PASS	post-authorisation safety study
PSUR	periodic safety update report
PUVA	psoralen ultraviolet A phototherapy
RA	rheumatoid arthritis
RMF	registry master file
RP	registry physician
RSF	registry site file
SAE	serious adverse event
SAP	statistical analysis plan
SIR	standardized incidence ratio
SSC	Scientific Steering Committee
TB	tuberculosis
TNF	tumour necrosis factor
UV	ultraviolet

Table 0-1: Registry Flowchart

	Data Collected		
	Enrolment	Year 1 – Year 2	Year 3 – Year 5[a]
Study Interval	Baseline	Every 3 months (± 4 weeks)	Every 6 months (± 4 weeks)
Visit ID	1	2 – 8	9 – 12
Informed consent/assent	X		
Patient/legal representative contact information	X	X	X
Demographics	X		
Medical history	X		
Co-morbidities	X	X	X
Psoriasis history (including date of diagnosis, severity assessment, previous treatments)	X		
Etanercept exposure	X[b]	X	X
Treatment discontinuation		X	X
Other systemic psoriatic treatments[b]	X	X	X
Prior medications	X		
Concomitant medications	X	X	X
Serious and pre-specified opportunistic infections[c]	X[b]	X	X
Malignancies[c]	X	X	X
Other adverse events[c]		X	X
Registry discontinuation[d]	0----------	----------	----------X

a. Patients enrolled after September 2013 may be followed for less than 5 years (i.e., until overall study completion in 2018)
b. For patients being treated with etanercept prior to enrolment, details regarding etanercept dose and regimen, other systemic treatments, and serious and pre-specified opportunistic infections occurring since the first etanercept dose but before enrolment will be collected via retrospective medical record abstraction.
c. Patients will be interviewed at the specified timepoints to determine if any of these events have occurred since the last evaluation. However, the registry physician may report an event between evaluations if he becomes aware that such an event has occurred.
d. Patients may discontinue from the registry at any time following enrolment.

1. INTRODUCTION

Psoriasis is a chronic, inflammatory, hyperproliferative skin disease with a genetic basis that affects approximately 2% of the world's population.[1,2] Dysregulation of T cell antigen-presenting cell interactions and over-expression of pro-inflammatory cytokines both play a central role in the pathogenesis of psoriatic skin lesions.[3] The clinical course is unpredictable, but in the majority of cases, psoriasis is a chronic, remitting and relapsing disease. Plaque psoriasis presents with characteristic plaque-type lesions, which consist of sharply demarcated, dull red scaly plaques, often symmetrically distributed over the body, particularly on the extensor surfaces of limbs and on the scalp.

The true incidence and natural history of paediatric psoriasis is poorly understood. It is reported that psoriasis represents 4.1% of all dermatoses seen in children under the age of 16 in Europe and North America, and that 30% to 45% of affected patients recall signs of disease before adolescence.[4,5] Data on childhood disease severity and treatment are also scarce. One study reported that ~8% of children had severe disease requiring phototherapy or systemic psoriasis therapies.[6] Quality of life in children and adolescents with severe psoriasis is reduced as the disfiguring consequences may cause severe psychological problems.[7] The epidemiology and natural history of psoriasis is better understood in adults, for which treatment algorithms and clinical guidelines exist.[8,9] In contrast, little is known about the disease in paediatric populations and we identified no treatment guidelines for paediatric psoriasis. A safe and efficacious treatment option for paediatric psoriasis patients with moderate-to-severe disease is thus an unmet medical need.

Current first-line therapies for plaque psoriasis include emollients, salicylic acid, topical corticosteroids, vitamin D analogues (for children ≥ 6 years), coal tar, dithranol and tazarotene (a topical retinoid). Calcipotriene and corticosteroid formulations are approved for the treatment of mild to moderate plaque psoriasis but may be inadequate in the treatment of moderate to severe psoriasis. Narrow band ultraviolet (UV) B phototherapy or a psoralen/ultraviolet A (PUVA) combination is limited in children because of concerns of carcinogenicity and premature aging. PUVA is used in adolescents only when absolutely necessary, but remains contraindicated in young children. Additionally, light therapies require frequent office visits, interfering with school and work schedules. Systemic treatments used for severe forms of plaque psoriasis that are resistant to other therapies include acitretin, cyclosporin, methotrexate, and biological therapies, such as adalimumab, alefacept, efalizumab, infliximab, not all of which are indicated for use in children.

1.1. Background and Rationale

Etanercept is a soluble tumour necrosis factor (TNF) receptor fusion protein previously indicated for the treatment of moderately to severe active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis in adults, as well as polyarticular juvenile idiopathic arthritis (JIA) (refer to Enbrel Summary of Product Characteristics, accessible at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000262/WC500027364.pdf). In November 1998, the US Food and Drug Administration (FDA) first approved etanercept for use in adults to reduce signs and symptoms of moderate to severe active rheumatoid arthritis (RA), in patients with an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Etanercept was subsequently approved for the treatment of moderate to severe JIA in children and adolescents (4-17 years of age) intolerant or responding inadequately to methotrexate. In patients with JIA, etanercept has also shown a favourable long-term safety profile, as repeated etanercept treatment (0.4 mg/kg twice weekly) for up to 8 years did not reveal an increase in serious adverse events.[10,11] Etanercept has shown a favourable risk-benefit profile in adults treated for moderate to severe plaque psoriasis and in patients as young as four years of age with JIA.

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 labelling for etanercept includes a black box warning addressing the risk of serious infections that may lead to hospitalisation 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 theoretically 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 tumours 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.

A recent Phase 3 clinical study was performed in support of adding an indication for moderate to severe plaque psoriasis in children and adolescents. The study reported statistically significant improvement in disease severity but was limited, by design, to short-term safety outcomes.[12] This 48 week randomised, placebo-controlled trial of the safety and efficacy of etanercept included 211 patients with moderate to severe plaque psoriasis between 4 and 17 years of age. During the first 12 weeks of the trial, patients received once

weekly injections of either placebo or 0.8mg/kg of etanercept, followed by an extension in which all patients received etanercept for 24 consecutive weeks. At week 36, 138 of the patients were randomised to receive placebo or etanercept to investigate the effects of stopping and re-starting treatment. The study showed that at 12 weeks, 57% of patients achieved 75% improvement in the psoriasis area-and-severity index compared with 11% of the patients receiving placebo. After 36 weeks, 68% of etanercept patients achieved improvement. Etanercept was well tolerated, and rates of infectious and non-infectious adverse events were comparable in the treatment and placebo arms. During the placebo-controlled stage of the study, there were no SAEs. Four SAEs including three severe infections (gastroenteritis, gastroenteritis-associated dehydration, and pneumonia) occurred during open-label treatment of three patients. All events resolved without sequels. Although no malignancies, opportunistic infections or cases of tuberculosis were reported during the study, it is also recognised that longer term data are required to better understand the risk of malignancy, the risk of serious infection, and other as yet unidentified events associated with potentially chronic use. It is expected that as etanercept is not curative, patients will receive repeat courses when disease flares occur. The risks associated with this type of chronic repetitive administration in children and adolescents with plaque psoriasis are not fully understood.

Following a positive recommendation from the 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 constitutes a post-authorisation safety study (PASS) and is a condition of marketing authorization, to be conducted in compliance with Volume 9A of The Rules Governing Medicinal Products in the European Union (EU) (Guidelines on Pharmacovigilance of Medical Products for Human Use) and 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.

2. STUDY OBJECTIVES AND ENDPOINTS

The objectives of this study are to:

- Describe the risk of serious and pre-specified opportunistic infections (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 unrecognised 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).

2.1. Endpoints

2.1.1. Safety Endpoints

Any patient who receives at least one dose of etanercept will be included in the evaluation for safety. Whenever a patient or parent/legal representative reports an event of interest directly to site staff or CRO registry staff, the registry physician (RP) will be contacted and asked to review records and confirm the occurrence and characteristics of the event. If needed, the RP will obtain records from other health care providers who may have treated the event of interest.

2.1.1.1. Serious and Opportunistic Infections

Serious infections

Serious infections are defined as any infections that are life-threatening or result in disability, and infections requiring intravenous antibiotic treatment and/or hospitalisation. Nosocomial infections that are included in the above definition will be categorized as such for purposes of analysis.

Opportunistic infections

Opportunistic infections of interest (i.e., pre-specified opportunistic infections) include the following listed infections and pathogens in Table 2-1.

Table 2-1: Opportunistic Infections

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			

2.1.1.2. Malignancies

If a malignancy occurs, the registry will collect reports of all solid malignant tumours, including non-melanoma skin cancers, and malignant tumours of haematopoietic and lymphoid tissues. In order to meet the case definition for malignancy, a pathology report or a physician's notation of specific tumour histology will be required.

2.1.1.3. Other SAEs and AEs

Reports of all other SAEs and non-serious AEs that occur during follow-up will be collected and described.

2.1.2. Effectiveness Endpoints

The primary focus of this registry is safety; it will not directly measure effectiveness endpoints. However, 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 24 weeks; physicians are advised to consider discontinuation of etanercept if a satisfactory response is not achieved by 12 weeks. If a patient receives etanercept for less than 24 weeks, the RP will be asked to report the reason for early discontinuation of therapy whether for positive (e.g., clearing of plaque psoriasis) or negative reasons (e.g., intolerance, adverse event, less than expected therapeutic effect). Treatment discontinuation for lack of desired therapeutic effect will, for purposes of analysis, serve as a proxy for treatment effectiveness.

As etanercept is not a cure for this chronic condition, patients will likely require repeated courses of etanercept over time. For each subsequent course of etanercept, occurrence and reasons for premature discontinuation, i.e., less than 24 weeks, will be documented. If a subsequent course of systemic therapy does not include etanercept, the reason for that decision will also be documented.

2.2. Concomitant Medications

Treating physicians will report information regarding use of medications and other treatment, including topical medications, and other immunosuppressant and immune-modulator medications.

The following information on other psoriasis treatments and concomitant medications will be included:

- Type of treatment (e.g., PUVA) or medication name
- Status of exposure to medication (i.e. current treatment, past treatment)
- Dose and duration of exposure
- Indication for use

3. STUDY DESIGN

This product registry is a multi-centre, long-term, prospective, observational, cohort study conducted to evaluate the long-term safety and effectiveness of etanercept prescribed by dermatologists to children for the treatment of plaque psoriasis. This registry constitutes a PASS and is a condition of marketing authorization, to be conducted in compliance with Volume 9A of The Rules Governing Medicinal Products in the European Union (EU) (Guidelines on Pharmacovigilance of Medical Products for Human Use).

It is estimated that during the first 4 years following approval for treatment of plaque psoriasis in patients aged 8 through 17, etanercept will be prescribed for approximately 250 patients throughout Europe. The registry will target recruitment of 60 to 80 patients.

The study will be performed by the CRO, with oversight of a project-specific Scientific Steering Committee (SSC), (refer to Section 10.2.2) and with guidance, input, review and approval by the Pfizer paediatric psoriasis registry project team.

4. STUDY POPULATION

4.1. Registry Enrolment

4.1.1. Geographical Scope of Registry

Paediatric plaque psoriasis is a rare disease for which actual prevalence data are sparse. In order to optimize registry enrolment and reach recruitment goals, systematic selection of participating EU countries and dermatology clinics will be guided primarily by the following criteria:

- Country-specific prevalence of psoriasis (this may be suggested by clinical sites within the country that already participate in an adult psoriasis registry);
- Local availability of etanercept for use in paediatric plaque psoriasis;
- High market penetration of etanercept in the country for other indications, including adult plaque psoriasis. While this will not guarantee use among dermatologists for paediatric plaque psoriasis, we believe physicians with familiarity with etanercept are more likely to prescribe it for this indication.

Due to the low prevalence of the disease in the paediatric population and the inability to predict the uptake of the product immediately after approval, committing to specific countries and sites is impractical at this time. It is currently estimated that a total of 11-15 EU countries and up to 100 dermatology clinics will be included; however, the number of countries and sites may be adjusted in order to meet enrolment objectives.

Upon selection of each country, the Sponsor will notify the respective National Responsible Person (NRP) and the EMA.

4.1.2. Physician Enrolment

The Sponsor will recruit dermatologists within the selected EU countries who are likely to treat patients eligible for the registry such as those treating paediatric patients and those known to prescribe etanercept for adult plaque psoriasis. The enrolled physicians are hereafter referred to as “registry physicians” or RPs.

4.1.3. Patient Enrolment

All paediatric patients undergoing treatment at any of the registry sites who meet the inclusion and exclusion criteria detailed above (see Section 4.2 and 4.3) may be included in the registry. Sites will be required to maintain a patient enrolment log of eligible patients at each treatment centre. This log will document how patients came to be included or excluded

from the registry, including patients identified by the site as initiating etanercept prior to registry enrolment, in order to assess the representativeness of the registry population. Patients treated with etanercept for plaque psoriasis but permanently discontinuing therapy prior to site participation in the registry are not eligible for inclusion.

An independent ethics committee (IEC) must review and approve the protocol, informed consent form (ICF) and paediatric assent forms before any patients are enrolled. Each patient and parent/legal representative must participate in the informed consent process and sign and date an ICF for this protocol before any data are collected and made accessible to the Sponsor. As required by local regulations, investigators will obtain paediatric assent. Throughout this document, the requirements for informed consent also apply to assent. The registry will require that documentation of informed consent and assent be recorded in the source documents for each patient.

It is anticipated that in most, if not all, countries in which the registry will be conducted the following requirements for inclusion of paediatric patients will apply:

- Patients < 7 years of age: written parental consent only to participate
- Patients age 7 and ≤ 17: written parental consent and paediatric assent to participate

These requirements must be adjusted by country and site to comply fully with local regulations and ethics committee requirements, as needed, such as in countries where older adolescents (e.g., > 15 years) are expected to provide written informed consent similar to adults, rather than assent. In some EU Member States, written informed consent from both parents may be required. If a paediatric patient reaches 18 years of age during registry follow-up, he/she will be asked to sign the current IEC-approved ICF at that time.

4.2. Inclusion Criteria

To be eligible for registry enrolment, patients must meet all of the following criteria:

- Age ≤ 17 years at time of administration of the first dose of etanercept
- Diagnosis of plaque psoriasis by a dermatologist
- Prior to enrolment, a clinical decision has been made to prescribe etanercept for the treatment of psoriasis
- Newly prescribed with initial etanercept or actively being treated with etanercept, regardless of length of treatment prior to study enrolment
- Capable and willing to provide paediatric assent, or written informed consent when applicable, and
- Parent(s)/legal representative of patient is capable and willing to provide written informed consent

- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study must exist.

Please note: Currently etanercept is approved for the treatment of severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The registry protocol will not encourage use of etanercept at younger ages. However if a doctor, in collaboration with the child's parents, makes the independent clinical decision to prescribe etanercept to a child less than 6 years of age for severe plaque psoriasis, that child may be included in the registry.

4.3. Exclusion Criteria

Patients are not eligible for this registry if they meet any of the following criteria:

- Prior therapy with any biologic agent other than etanercept
- History of malignancy
- Unlikely to complete a minimum of two years of follow-up, based on physician's judgment (i.e., social issues, family illness, plan to move out of area, living too far from the physician's office to adhere to standard of care visit schedule)
- Participation in any study involving any experimental drug or device within the last 30 days or 5 elimination half-lives, whichever is greater
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

5. STUDY TREATMENT AND DURATION

There will be no dispensing of any study medication or protocol-specified procedures associated with participation in this registry. All medical treatment, including medications, is solely at the discretion of the treating physician in accordance with their usual care.

The total duration of the registry is approximately 9 years, including approximately 4 to 5 years for patient enrolment and 4 to 5 additional years for follow-up on all enrolled patients. Dermatologists will enrol eligible patients who are current users of etanercept at any time after they initiate such treatment for plaque psoriasis. The Sponsor expects to enrol the first patient in Q4 2010, with all follow-up to be completed in 2018. Follow-up will occur every 3 months during the first 2 years of the study and every 6 months thereafter (year 3 through the end of participation). Each patient is expected to participate for 5 years, or until the registry is completed in 2018, whichever comes first.

6. STUDY PROCEDURES

6.1. Schedule of Assessments

For the purpose of routine clinical care of chronic psoriasis, it is anticipated that follow-up with the treating physician will occur at least once every 3 months for the first two years after receiving the first dose of etanercept at which time RPs will collect follow up data. Alternatively, the patient and the parent/legal representative may be contacted by phone. Thereafter, data collection will take place every 6 months (also in conjunction with routine clinical visits) from year 3 through the end of follow-up, as shown in the registry flowchart. The registry will allow a window of ± 4 weeks around the date of the scheduled data collection. Infections, malignancies, SAEs, etanercept discontinuations and registry discontinuations may be reported at any time during follow-up.

At each scheduled data collection point, the RP will record information on the registry outcomes of interest, comorbid medical conditions, medication use, and SAEs. In order to maximise retention and capture relevant data, a highly structured approach to managing follow-up is planned. Centralised registry resources will proactively contact sites (quarterly during the first 2 years, semi-annually thereafter) in advance of scheduled data collection times to remind the RP to collect and report study data. At that time, registry staff will update contact information regarding the patients and their physicians. If data has not been received within the expected timeframe, CRO will contact sites several times following the original due date. They will make every reasonable effort (including direct-to-patient calls) to obtain this data before considering a patient lost to follow-up. For each site, the electronic data capture (EDC) system will also provide active, up-to-date workflow reports alerting them to upcoming and overdue timepoints.

If, during the study period, the enrolled site is not actively following the patient, CRO will provide the enrolled site with the contact information for the patient's primary health care provider (or other treating physician) and a standard form letter (with a paper copy of the questionnaire) that the site can fax/mail to the physician requesting the follow-up information on behalf of the registry. The patient's treating physician will be asked to complete the questionnaires and return them to CRO for data entry.

6.2. Data Collection

Data collection is designed to minimise the burden on the participating RPs and patients, and maximise retention. Electronic case report form for data entry, are designed to elicit the specific desired data points.

Data will be collected from the following sources:

- Prospective data provided by the treating physicians (this may be multiple physicians including the prescribing dermatologist or RP, and other physicians responsible for the patient's care over the course of the study);
- Prospective data collected from patient interviews during the less frequent follow-up phase of the study.
- Retrospective data collected by medical record abstraction

The RP will provide information on current prescriptions and status of each registry patient at enrolment and at each scheduled follow-up assessment. Following enrolment in the registry, the RP will also provide information by retrieving medical record information at his/her own institution and other health care settings, as appropriate. Some patients may be undergoing active treatment with etanercept at the time of registry enrolment, and the lag between initiating etanercept treatment and active data collection as part of the registry will necessitate the abstraction of relevant safety-related and treatment pattern information from the medical record. The number of patients meeting this criterion is expected to be limited.

6.2.1. Baseline Visit

During the enrolment visit, the site will be instructed to obtain additional information regarding the patient, including secondary contact information and contact information for the patient's primary health care provider.

The following information will be collected:

1. Date of informed consent(s)/assent
2. Patient/legal representative contact information, including secondary contacts and primary health care provider details, if different than RP
3. Demography [age, gender, weight, race/ethnicity (where allowed by local regulation)]
4. Medical history/co-morbid medical conditions
5. Plaque psoriasis history
    a. Physician's global subjective assessment of disease severity (four-point scale)
    b. Prior treatments or therapies, including topical agents and immunosuppressive therapies and the patient's response to each.
6. Etanercept Treatment
    a. Initial prescribed etanercept treatment regimen
    b. Date of first dose
7. Concomitant medications, including immunosuppressants
8. Retrospective medical record abstraction for patients with historical treatment with etanercept will also include:
    a. Etanercept dosing history
    b. Use of additional systemic therapies since starting etanercept
    c. Occurrence of serious and/or pre-specified opportunistic infections and SAEs

Note: Due to the significance of the AEs of interest (serious and opportunistic infections and malignancies), it is considered highly likely that these events, if they occurred, would be documented in the medical record of the prescribing RP. Retrospective data for other SAEs overall, however, may not be consistently recorded; therefore, all retrospective SAEs will be collected but analysed separately.

6.2.2. Follow-up Visit

FOLLOW-UP: YEAR 1 THROUGH 2

Regardless of the duration of etanercept exposure at the time of registry enrolment, all patients will be followed prospectively using the same schedule. During follow-up, the RP or other trained site staff will collect data during routine clinical visits. Routine clinical visits may not coincide with registry timepoints; therefore alternatively, the RP, trained site staff or CRO registry staff may administer follow-up questionnaires via phone interviews.

The following data will be collected every 3 months (± 4 weeks) during the first 2 years of participation:

1. Updated informed consent information (e.g., if patient turns 18 since last follow-up)
2. Updated contact information
3. Status of etanercept exposure (ongoing/completed/discontinued/reason for discontinuation)
4. Requirement for additional psoriasis treatment
    a. Continued etanercept
    b. Other systemic treatments
    c. Use of topical agents
    d. Reason for treatment decision
5. Physician's global subjective assessment of plaque psoriasis severity
6. Changes in medical status, including new onset comorbid medical conditions
7. Changes/additions to concomitant medications
8. AEs as described in Section 2.1.1, Safety Endpoints
    a. Serious and pre-specified opportunistic infections
    b. Malignancies
    c. Other AEs

FOLLOW-UP: YEAR 3 THROUGH YEAR 5/END OF FOLLOW-UP

The following data will be collected every 6 months (± 4 weeks) during year 3 through the end of participation:

1. Updated informed consent information (e.g., if patient turns 18 since last follow-up)

2. Updated contact information
3. Status of etanercept exposure (ongoing/completed/discontinued/reason for discontinuation)
4. Requirement for additional psoriasis treatment
    a. Continued etanercept
    b. Other systemic treatments
    c. Use of topical agents
    d. Reason for treatment decision
5. Physician's global subjective assessment of plaque psoriasis severity
6. Changes in medical status, including new onset comorbid medical conditions
7. Changes/additions to concomitant medications
8. AEs as described in Section 2.1.1, Safety Endpoints
    a. Serious or pre-specified opportunistic infections
    b. Malignancies
    c. Other AEs

6.2.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural, or administrative reasons. Patients and/or their respective parents/legal representatives if minors have the right to withdraw from the registry at any time, without prejudice, and are not obligated to state their reasons for registry discontinuation. If a patient or parent/legal representative declares his or her wish to discontinue from the registry, the RP will complete a discontinuation CRF. All reasonable efforts will be made to establish whether the reason for discontinuation was related to a registry outcome of interest or other adverse event. The Sponsor reserves the right to suspend or terminate the registry or part of the registry at any time for any reason.

Before considering a patient lost to follow-up, the RP/site staff will make all reasonable attempts to contact the patient or the parent/legal representative to ensure that a registry outcome of interest is not the underlying reason for the inability to contact the patient. For each missed scheduled encounter with the RP, several attempts to reach the patient by phone, e-mail and post will be made with a minimum of three attempts and a period of approximately one week between attempts. If no response is received within a month of the follow-up timepoint, CRO registry staff will contact any other known healthcare providers to determine if the reason for failure to respond is health-related, and to determine the health status of the patient. If CRO is unable to obtain the follow-up data from the RP or other provider(s), they will contact the secondary patient contact to obtain vital status. The informed consent process and forms will describe these procedures, including the possibility

of contacting the patient's non-RP health care providers. Data collected prior to loss to follow-up will be included in all analyses.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. DATA ANALYSIS/STATISTICAL METHODS

The purpose of the registry is to assess the long-term safety of etanercept in paediatric patients with plaque psoriasis and to infer effectiveness by describing the pattern of treatment of psoriasis in this population.

7.1. General considerations

All AE verbatim terms will be recorded and coded using MedDRA. Statistical analysis of all data will be performed using SAS® statistical software (SAS Institute, Cary, NC, USA).

Frequencies of defined outcomes will be described. If possible, analyses will also be performed using the different etanercept treatment status (i.e., current/recent versus past treatment) and etanercept cumulative dose exposure groups.

Analysis of the characteristics of patients enrolled in the registry and of those who did not consent to participate (to the extent feasible) will help evaluate whether there are any differences between registry enrolees and non-respondents, i.e., generalizability.

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 summarized separately.

7.2. Sample Size Calculation

No formal sample size calculation will be used to manage enrolment in the study since the goal is to obtain participation by all eligible patients. Current available data are insufficient to project population based estimates of paediatric patients with severe psoriasis treated with conventional systemic therapy who are not well-controlled and may warrant further intervention such as that potentially afforded by etanercept.

7.3. Baseline Assessment

The demographic and clinical profile of the registry population will be described using baseline data. Patient demographics, psoriasis severity, history of psoriasis and psoriasis treatment(s) prior to first etanercept administration will be summarized. Data will be

summarized overall and by status at enrolment to explore whether the patients treated prior to registry enrolment are different than the overall population.

Continuous variables (e.g., age) will be reported as means and standard deviations. Categorical variables (e.g., gender) will be summarized as number and percentage (%) of the total registry population.

7.4. Primary Analyses

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 24 weeks. Patients successfully responding to the first etanercept treatment course may be exposed to subsequent treatment (i.e., when patients experience a flare) and the time window between two (or more) consecutive courses of treatment may vary substantially.

Patterns of treatment with etanercept will be described (to the extent possible) as follows:

- Frequency of premature discontinuation of etanercept (i.e., treatment course < 24 weeks)
- Frequency of subsequent treatment with systemic therapies (including re-treatment with etanercept)
- Intervals between etanercept treatment and subsequent course of systemic therapy (including etanercept)
- Means and percentages of demographic and disease characteristics of patients who experience and those who do not experience discontinuation of etanercept
- Frequency of discontinuation stratified by cumulative dose, duration of use, and other etanercept use patterns.

Serious and Pre-specified Opportunistic Infections

Time at risk of serious and pre-specified opportunistic infections will correspond to current/recent treatment with etanercept. Current/recent etanercept treatment will be defined as time between the dates of first and last dose within a treatment course plus 28 days. Risk will be estimated as number of events over cumulative time at risk. Estimates of relative risk of these infections will be used to quantify any association between the study outcomes and current/recent treatment with etanercept. In order to calculate relative risk, incidence of infection during cumulative current/recent treatment with etanercept will be compared to incidence of infection during cumulative period without use of etanercept.

Should any patient develop tuberculosis (TB) during the course of follow-up, the Sponsor will conduct standardised incidence ratio (SIR) analyses using geographically appropriate population based rates of TB applied to time at risk on etanercept.

Analyses may include more than one episode of infection experienced by a single individual. Stratified analyses of the events of interest by etanercept dose, duration of treatment, and

number of treatment course (i.e., first, second, etc.) will be attempted, depending on the number of events reported.

Malignancies

Time at risk of incident malignancies will be defined as time since the date of first dose of etanercept treatment to the date of malignancy diagnosis or end of follow-up if no malignancy has been diagnosed. Long-term risk of incident malignancy in patients who have ever received etanercept will be estimated as number of events over the total time at risk. Should any patient develop cancer during follow-up, the Sponsor will calculate SIRs for malignancy (age and gender-adjusted) using geographically appropriate population-based norms. Although all malignancies reported throughout the study will be described, only the first diagnosis of malignancy occurring during the follow-up will be considered in the SIR analysis.

Other SAEs

Time at risk of all other SAEs will correspond to current/recent treatment with etanercept. Current/recent etanercept treatment will be defined as time between the dates of first and last dose within a treatment course plus 28 days.

A descriptive analysis of SAEs will be conducted. Any grouping and stratification will be dependent on the number and type of events reported.

7.5. Missing Data

Several attempts will be made to contact patients and to limit missing data. Some imputation (e.g., in order to estimate minimum and maximum exposure) may be required. Details on handling of missing data will be included in the statistical analysis plan (SAP).

7.6. Limitations of the Registry

The planned registry offers as strengths the long-term follow-up during and after treatment with etanercept in a population of paediatric psoriasis patients in the EU. Such a setting will allow fulfilment of the objectives of this registry. However, the registry also carries some limitations. As in any registry, lack of an internal ‘untreated’ contemporaneous comparator group may pose some challenges for the interpretation of data. In the evaluation of the risk of serious and pre-specified opportunistic infections, an attempt will be made to make comparisons within the registry population based on current/recent treatment and periods without etanercept treatment. However, such an approach is unfeasible when assessing risk of malignancies and appropriate external comparator groups will be needed to aid in the interpretation of the registry data. Generalizability of the results may be limited by the characteristics of the population that voluntarily enrol in the registry. Attempts will be made

to characterize and compare patients who refuse to participate with patients who agree to enrol in the registry.

The registry will include patients who initiated etanercept prior to enrolment into the registry. There is the possibility that these patients, who must be considered actively treated at the time of enrolment, are substantively different than other patients who were prescribed etanercept at the same time, but did not tolerate therapy or experienced one or more relevant SAEs, potentially resulting in a differential depletion of susceptible (i.e., the effect whereby patients who remain on treatment are those who can tolerate them while those who are susceptible select themselves out of the population at risk). This could lead to an underestimation, or dilution, of the estimated risk of developing an adverse event associated with etanercept in the population with retrospective data collection.

Generalizability of the results may be limited by the characteristics of the population that voluntarily enrol in the registry. Attempts will be made to characterize and compare patients who refuse to participate with patients who agree to enrol in the registry.

8. DATA COLLECTION AND DATA MANAGEMENT

8.1. Operations

Each participating site will receive appropriate training, which describes all processes that the RP or representative must understand. The information will outline all processes required for a clinic to become a registry site, enrolling patients, providing follow-up data on enrolled patients, maintaining registry documents or files, reporting adverse events and closing the registry. All site staff who participates in enrolling patients, collecting or entering data for the registry will be required to undergo appropriate training.

8.2. Required Documentation

The RP must provide the Sponsor with the following regulatory documents before enrolling any patients:

- Current signed and dated curricula vitae for the RP and site staff having significant responsibility (i.e., those related to determination of eligibility or safety)
- Copy of the IEC approval letter for the protocol and informed consent. All written information provided to the patient must be approved by the IEC
- Copy of the IEC-approved informed consent document to be used
- Copy of the protocol sign-off page signed by the investigator
- Fully executed site agreement

8.3. Data Entry

All data will be collected and entered by the RP/participating sites directly into the EDC system. All sites will be fully trained on using the on-line data capture system, including

eCRF completion guidelines and help files. Sites will have the ability to add a new record, to search for and modify existing records, to search for patients for whom follow-up is due, to identify records with outstanding queries and to identify records that require signatures.

Data collected by the RP, including data collected from interview of patients or their parents/legal representative will be entered into a validated database. All data entry will be conducted so that errors in data completeness, data validity, and data consistency are minimized. It is the RP's responsibility to ensure the accuracy of the data provided to the registry by any site staff that is trained for registry data collection.

On a regular basis, when analysis is planned and after quality assurance procedures have been completed, the database will be frozen and a dataset created so that no further changes take place and analysis can be implemented.

8.4. Case Report Form

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialled and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

8.5. Patient Files

The RP and trained staff at the registry sites will maintain files on each enrolled patient. In addition, all original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The RP will be instructed to notify Pfizer before any destruction of medical records of registry participants. If an RP becomes involved in follow-up with other clinicians, the associated documentation provided by other clinicians will be maintained in the patient's registry file at the site.

8.6. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

The RP at each registry site will receive a registry site file (RSF) upon initiation of the Registry. This RSF will contain all documents necessary for the conduct of the registry and will be updated and completed throughout the study. The RSF must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 5 years after the completion the registry. Documents to be archived include the patient enrolment log and the signed patient ICFs. In the event that archiving of the RSF is no longer possible at the site, the RP will be instructed to notify Pfizer.

The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.7. Quality Assurance, and Inspection by Authorities

The registry database will be housed at the CRO in a physically and logically secure computer system maintained by the CRO in accordance with its written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Committee on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the eventual registry report, is subject to independent clinical quality assurance audits. Audits

may be conducted by the Sponsor, or its designated organization, at any time during or after registry initiation to ensure the validity and integrity of the registry data. In addition, the Registry may be inspected by health authorities.

9. ADVERSE EVENT REPORTING AND SERIOUS ADVERSE EVENT REPORTING

ADVERSE EVENTS

All observed or volunteered adverse events regardless of treatment group (if applicable) or suspected causal relationship to etanercept will be recorded on the adverse event page(s) of the case report form (CRF) as follows.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (see section "Serious Adverse Events") requiring immediate notification to Pfizer or a Pfizer-designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to etanercept, follow-up by the investigator is required until the event or its sequels resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

All AEs must be evaluated by the site and assessed for seriousness, as defined below in Section 9.1.

REPORTING PERIOD

All reportable serious and non-serious AEs directly observed or reported by the patient or caregiver to the physician or other site personnel, from the time of enrolment (i.e., informed consent has been obtained and the patient has received at least one dose of etanercept) through patient discontinuation from the registry, end of the observation period, or 28 days after the last dose of etanercept, whichever is later, will be assessed and recorded, if applicable, within the CRF. If a patient was administered etanercept on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. The site will record the diagnosis, if available. If no diagnosis is available, the site will be instructed to record each sign and symptom as an individual event.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to etanercept, the SAE also must be reported to Pfizer Safety.

Specific AE data (i.e., serious infections, pre-specified opportunistic infections, and malignancies) will be obtained at scheduled or unscheduled interviews based on information provided spontaneously by the patient (or parent) and/or by thorough questioning of the patient (or parent). To elicit reports of these events, each interview will begin with simple open-ended questions and questions designed to collect information regarding the specific outcomes of interest.

If a patient is seen by a non-RP physician or hospitalised in relation to an AE, the RP or trained registry site personnel should, in a timely manner, make every effort to follow-up with the treating physician or relevant concerned health care provider to obtain all information necessary for the accurate reporting of the event.

For instances where an event is reported by the patient and/or treated by a non-RP, registry staff will contact the treating physician or other health care provider as described and authorized by the informed consent, in order to obtain relevant information necessary for complete reporting of adverse events.

9.1. Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event)
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease
- Lack of efficacy
- Drug abuse
- Drug dependency

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
-

- Drug misuse
- Drug interactions
-
- Extravasation
- Exposure during pregnancy
- Exposure during breast feeding
- Medication error
- Occupational exposure

ABNORMAL TEST FINDINGS

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

A **serious adverse event** (SAE) is any untoward medical occurrence at any dose that:

- Results in death.
- Is life-threatening as it occurred, i.e, the patient was at risk of death at the time of the event. This does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation (see below for circumstances that do not constitute adverse events) .
- Results in persistent or significant disability/incapacity, defined as a substantial disruption of a patient's ability to conduct normal life functions.
- Results in a congenital anomaly or birth defect.
- Constitutes an important medical event, i.e, based upon appropriate medical judgement, event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

HOSPITALIZATION

AEs reported from studies associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g.,, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

If there is any doubt about whether the information constitutes an AE, the information will be treated as an AE. Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

CAUSALITY ASSESSMENT

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). The investigator must record the causal relationship in the CRF, as appropriate, and

report such an assessment in accordance with the serious adverse reporting requirements if applicable.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that etanercept caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether etanercept caused the event, then the event will be handled as related to etanercept for reporting purposes. If the investigator's causality assessment is unknown but not related to etanercept this should be clearly documented in the CRF.

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, lack of efficacy, and occupational exposure are described below.

EXPOSURE DURING PREGNANCY

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) etanercept, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to etanercept (maternal exposure).

2. A male has been exposed, either due to treatment or environmental, to etanercept prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source is reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If any study patient or study patient's partner becomes, or is found to be, pregnant during the study patient's treatment with etanercept, the investigator must submit this information to Pfizer within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred, using the NIS AEM Report Form and the EDP Supplemental Form.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain pregnancy outcome information on all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (e.g., induced abortion) and then notify Pfizer of the outcome. The

investigator will provide this information as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner

EXPOSURE DURING BREASTFEEDING

Scenarios of exposure during breastfeeding must be reported to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE.

MEDICATION ERROR

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer)
- Confusion with regard to invented name (e.g., trade name, brand name)

The investigator must submit the following medication errors to Pfizer within 24 hours of awareness, irrespective of whether an adverse event occurred:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE
- Medication errors including potential medication errors or near misses that do not involve a patient directly. When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report
  - An identifiable reporter
  - A suspect product
  - A medication error including potential medication error or near miss

LACK OF EFFICACY

Reports of lack of efficacy to etanercept are to be submitted to Pfizer by the investigator within 24 hours of awareness, irrespective of the presence of an associated AE/SAE or the indication for use of etanercept.

OVERDOSE AND MISUSE

The investigator must submit reports of overdose and misuse associated with the use of etanercept to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE/SAE.

OCCUPATIONAL EXPOSURE

Reports of occupational exposure to etanercept are to be submitted to Pfizer by the investigator within 24 hours of awareness, irrespective of the presence of an associated AE/SAE.

9.2. Adverse Event and Serious Adverse Event Recording and Reporting

Complete training on AE and SAE reporting practices will be provided to each participating site. Any AE/SAE observed by or reported to site personnel by the patient that occurs from the time of enrolment through patient discontinuation from the registry, end of the

observation period, or 28 days after last dose of etanercept, whichever is later, is potentially reportable. The RP must instruct the patient to report AEs (including SAEs, AEs of special interest and non-serious AEs)(see list under Section 9.1) during this time period.

Each AE is to be assessed to determine if it meets serious criteria. If a SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition of SAE, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

This study protocol may require review of the patient medical chart. Review of patient medical charts for specific attribution of SAEs to Pfizer drugs will not be actively pursued. However, while the primary purpose of this study does not encompass assessment of drug-related effects in individuals, the reviewer may identify an SAE with explicit attribution to a Pfizer drug via patient chart (and with an identifiable reporter). Such SAEs must be reported to Pfizer or its representative for submission to regulatory authorities. Explicit attribution is not inferred by a temporal relationship between drug administration and an SAE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the SAE.

If there is a written notation in the medical chart indicating that a physician attributed a serious or non-serious adverse event to a Pfizer drug, Pfizer or its representative/the reviewer will record the event on the CRF, and report SAEs and non-serious AEs of interest, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

SERIOUS ADVERSE EVENT REPORTING REQUIREMENTS

If a SAE occurs, Pfizer is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure during breast feeding and medication error cases.

In the rare event that the investigator does not become aware of the occurrence of a SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the SAE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

The CRO EDC System will include a AE/SAE CRF for site staff to record basic information for any reportable AEs noted by the site or reported to the site by the patient. Entry of the CRF will generate an automated notification to CRO's registry staff to ensure appropriate follow up.

Recording of AEs/SAEs on the CRF does not satisfy the requirements for expedited reporting of events for regulatory reporting purposes.

The site is also required to fax a completed Non-Interventional Study (NIS) AEM Report Form to CRO each time a SAE or an AE of interest is reported. The document will then be transmitted to Pfizer's Drug Safety Unit within 24 hours for further processing and evaluation.

In case a pregnancy should be reported, site will complete a NIS AEM Report Form as well as the EDP Supplemental Form. Upon receipt of an automated email notification, if follow-up required, the CRO will immediately contact the site and request that the required Form(s) containing the minimum information (reportable event, identifiable subject, identifiable reporter and exposure to etanercept), is faxed to the CRO without delay. Upon receipt of the Form(s), the CRO immediately faxes it (them) to Pfizer local Drug Safety Unit (DSU), even

if minimal information is missing. The CRO then forwards the information to the Medical Monitor at the CRO via email.

All SAEs, pregnancies and AEs of interest (as listed under Section 9.1), and follow-up information must be reported within 24 hours by faxing a completed NIS AEM Report Form to the study center at CRO and confirming by phone or e-mail that the fax was received.

Additionally to the NIS AEM Report Form, pregnancy should also be reported using the EDP Supplemental Form.

All NIS AEM Report Forms and EDP Supplemental Forms should be faxed to the study center at CRO.

In order to maintain compliance with the EMA and other international regulatory bodies, sites may be further contacted by the registry staff or Pfizer safety personnel in order to collect additional information required to evaluate a potential SAE.

It is the responsibility of the site to inform their IEC (or equivalent local body governing research) of relevant SAEs occurring at their site, according to local requirements. Pfizer or CRO will notify the sites of any emergent product-related safety issues in accordance with local requirements.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g.,, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of etanercept, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

10. ETHICS

10.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

10.1.1. Study Approval

IEC approval consistent with local regulations will be obtained. Prior to enrolment of patients at a given site, the registry protocol will be submitted together with its associated documents (e.g., ICF, questionnaires) to the responsible IEC for its review. The written favourable opinion/approval of the IEC will be provided to each RP, and a copy will be filed in the Registry Master File (RMF) maintained by CRO.

Patient enrolment will not start at any site before the Sponsor has obtained written confirmation of a favourable opinion/approval from the concerned IEC. The IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favourable opinion/approval that clearly identifies the registry, the protocol version, and the Patient Information and Consent Form version reviewed will be provided.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the registry in accordance with local regulations and requirements.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.1.2. Amendments to the Protocol

Once the protocol has been approved by the local site IRB, the site investigators will not modify it. The site investigators will be notified in writing of any amendment(s) to the protocol and/or the informed consent form or assent form. Changes to the protocol will be documented in written protocol amendments. The protocol amendments will usually require submission to the Competent Authorities and to the relevant IECs for approval or favourable opinion. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained.

Any amendment that could have an impact on the patient's agreement to participate in the registry, e.g., changing the nature of the data collected, requires the patient's or parent/legal representative's informed consent prior to implementation.

10.2. Ethical Conduct of the Study

10.2.1. Guiding Principles

The registry will comply with VOLUME 9A of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use –Part 1 Section 7, Company-Sponsored Post-Authorisation Safety Studies.[13]

To ensure the quality and integrity of research, this registry will be conducted under the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for

Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.[14,15]

10.2.2. Opinion of External Experts and Scientific Boards

A Scientific Steering Committee (SSC), consisting of 5-7 external advisors, will be identified and recruited to assist in the study execution and interpretation. Specifically, physicians with expertise relevant to this effort, e.g., dermatology, general paediatrics, will be recruited. The Scientific Steering Committee will meet at pre-specified intervals and will be guided by a charter agreed upon at the start of the registry. They will review interim data on a regular basis to assess whether any developing safety signals are potentially associated with use of etanercept in this population.

In addition, an Endpoint Committee (EC) comprised of three (3) dermatologists or paediatricians will ensure that all events reported to the registry are evaluated and classified in a systematic manner. Two members will independently evaluate all reports of serious and pre-specified opportunistic infections, malignancies, and SAEs. Any discordant evaluations will be referred to a third member for independent review.

10.3. Patient Information and Consent

An unconditional prerequisite for a patient's participation in the registry is his or her informed consent. Since the registry will enrol children and adolescents, in most cases a written informed consent will be required from a parent/legal representative. Underage patients, as defined by local regulations in each of the selected countries, will be required to provide assent for participation. Underage patients that reach the local legal age for providing informed consent during follow-up will be re-consented as soon as feasible, i.e., at the next follow-up timepoint.

The RP will obtain informed consent for enrolment into the registry, including contact information for treating physician(s) other than the RP and permission to access hospital records, before any registry-related activities to collect data from or about that patient are carried out. Depending on the local regulations, the form may include consent for direct contact with the patient or parent/legal representative, and retrieval of information or supportive documentation from health care providers and/or administrative sources other than the RP.

Upon recruitment, the RP will be required to provide patients or parents/legal representatives with an information sheet in their local language that contains adequate information on risks of registry participation, in this case, limited to communication of personal identifiers and health information. If local regulations allow, provision of verbal and written information for the purposes of obtaining consent may be performed by a trained designee of the RP. Since

the registry will enrol a paediatric population, the language used to describe the registry must be cognitively understandable to children and adolescents.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The ICFs must be signed and personally dated by the patient, or a parent/legal representative, and the RP (or designee, if applicable). The signed and dated declaration of informed consent will remain at the RP's clinic and must be safely stored, so that the forms are retrievable at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and consent form will be provided to the patient or parent/legal representative.

Whenever important new information that may be relevant to patient's consent becomes available, the written patient information sheet and any other written information provided to patients or parents/legal representatives will be revised and submitted to the IEC. The agreed upon and approved, revised information will be forwarded to each patient or parent/legal representative in the registry. The RP will explain to the patient and/or parent/legal representative the changes to the previous version.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

10.4. Patient Identification and Privacy

After providing written informed consent, each patient will be assigned a unique registry patient identification number to be used throughout the study. This unique registry patient identification number will consist of the protocol number, site number (four digits), and patient number (three digits). All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

Example: the P patient enrolled at site PP in country PP in protocol B1801035

Protocol No.	Site No.	Patient No.
B1801035	PPD	PP

Should the patient be withdrawn from the registry, his or her unique patient identification number will not be reassigned.

Each patient's data collected in the registry will be stored under the unique registry patient identification number. To maintain privacy, personal contact information will be stored so that patients can be contacted regularly if necessary, but contact information will be stored securely and separately from all other data collected in the registry. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data.

In accordance with local regulations in each of the registry countries, patients or parents/legal representatives will be informed about data-handling procedures and asked for their consent. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on the protection of individuals, and in compliance with Safe Harbour privacy principles.[16,17]

10.5. Compensation to Patients and Physicians

One of the threats to any long-term cohort study is loss to follow-up. The ability to retain patients and physicians over multiple years is essential to meet the registry's goals. The study design has taken into account tracking and participation considerations that aim at maximising both aspects while preserving the validity of the registry.

To maximise patient retention, it is important to develop and maintain rapport between the RP and the patients/parents. In addition, if approved by the IEC, retention strategies may include the provision of general (i.e., not etanercept-specific) educational materials about psoriasis, feedback to patients about the registry progress, and nominal cash compensation for time spent completing registry-related questionnaires. We anticipate that such compensation, which would have a maximum cumulative value of 50 euros (or local equivalent), would be dispersed over the course of the registry observation period. It is important to emphasise that any such compensation would be independent of current psoriasis treatment; it is not an inducement to continue etanercept treatment but rather to maximise capture of follow-up information over the 5-year study, information that is critical for its success. Such patient remuneration would be explicitly explained in the informed consent, and would only occur with prior approval of local IECs. As a final strategy for registry enrolment and retention, we will also explore endorsement of local and national psoriasis patient groups.

The physicians will be compensated for their time to complete the registry requirements, consistent with local prevailing conditions. This compensation schedule will also be subject to local ethical committee approval.

11. COMMUNICATION AND PUBLICATION OF STUDY RESULTS

At the completion of the study, the final results will be disseminated publicly. Medically important findings that have public health impact identified prior to completion of the study will be communicated to regulatory agencies and the public according to regulatory and scientific guidance in a timely manner.

The Sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results. Publications will follow the International Committee of Medical Journal Editors guidelines[18], STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines[19], and GPP.[20]

Scientific peers shall be informed of study results in a timely fashion by publication in the scientific literature and presentations at scientific conferences, workshops, or symposia. Presentations at meetings should not be considered as a substitute for publications in the peer-reviewed literature. Authorship of study reports will follow the guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Potential conflicts of interest, financial and non-financial, should be disclosed.

If appropriate, methodology and special findings may be submitted for presentation. The publications will most likely include data from all registry sites.

11.1. Communication of Results by Pfizer

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of this study on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:

- Studies that Pfizer registered on www.clincaltrials.gov regardless of the reason for registration; OR
- All other studies for which the results have scientific or medical importance as determined by Pfizer.

Results are posted in two formats:

- The results of studies applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA) and/or An Act Regarding Advertising by Drug Manufacturers and Disclosure of Clinical Trials (state of Maine Reporting Requirements) are posted on ClinicalTrials.gov in a tabular format called Basic Results.

- The results of all required studies (even if not previously registered to ClinicalTrials.gov) and any voluntarily registered studies are posted on ClinicalStudyResults.org in a format called a Pharmaceutical Research and Manufacturers of America (PhRMA) website synopsis (PWS), the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products already approved in any country and applicable under FDAAA and/or state of Maine, Pfizer posts results within one year of the primary outcome completion date (PCD). For all other studies that do not involve a Pfizer product, Pfizer posts results one year from last patient last visit (LPLV);

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.

11.2. Enrolment and Progress Reports

The number and percentage of patients enrolled and patients discontinued from the registry will be summarized at periodic intervals, every six months for the first three years, and annually thereafter. Also, early identification of potential demographic and clinical differences between patients that enrol in the registry and those who choose not to enrol, or cannot be contacted, will be attempted.

11.3. Annual Analyses and Reporting

Annual reports will be generated beginning one year after start of enrolment (i.e., Q4 2010). The baseline characteristics of patients will be described. Demographic characteristics (e.g., age, gender) and disease characteristics (e.g., psoriasis treatment history, severity of psoriasis) will be presented using descriptive statistics for continuous variables or proportions for categorical variables. The median and mean follow-up time in the registry will be presented. Analyses of the outcomes of interest will be performed, dependent on the quantity of data available.

11.4. Final Analyses and Reporting

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, including a description of the complete registry population and estimates of events rates, as described above and in the SAP.

11.5. Reporting to the EMA

Following Competent Authority acceptance and unless otherwise requested, Pfizer will provide interim progress reports annually and the final report at the completion of the nine year registry, to the EMA as part of the Periodic Safety Update Report (PSUR) and updated etanercept risk management plans.

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