A non-interventional, post authorization safety study (PASS) to evaluate the safety of Kineret in the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in routine clinical care with regard to serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including re-use of syringe.

EU PAS Register No: ENCEPP/SDPP/6366

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Signatures of final protocol: Sobi.Anakin-201

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PASS information

Title	A non-interventional, post authorization safety study (PASS) to evaluate the safety of Kineret in the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in routine clinical care with regard to serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including re-use of syringe.
Protocol version identifier	Sobi.Anakin-201
Date of last version of protocol	10 June 2014
EU PAS register number	ENCEPP/SDPP/6366
Active substance	Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors, ATC code: L04AC03 anakinr**a**
Medicinal product	Kineret® 100 mg/0.67 ml solution for injection in pre-filled syringe
Product reference	EU/1/02/203/005 – 1-pack EU/1/02/203/006 – 7-pack EU/1/02/203/007 – 28-pack
Procedure number	EMEA/H/C/000363/X/0042
Marketing authorization holder	Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden
Joint PASS	No
Research question and objectives	The primary objective of the study is to evaluate the safety of Kineret treatment in CAPS patients in routine clinical care with focus on serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including re-use of the syringe.
Countries of study	The study is planned to start in UK, France and the Netherlands with the possibility to add countries later on (e.g. Italy).
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2 List of abbreviations

Abbreviation	Term
AE	adverse event
CAPS	Cryopyrin Associated Periodic Syndromes
CINCA	Chronic Infantile Neurological Cutaneous Articular syndrome
eCRF	electronic case report form
DMP	data management plan
EC	ethics committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS register	EU electronic register of post-authorization studies
FCAS	Familial Cold Autoinflammatory Syndrome
FDA	US Food and Drug Administration
ICF	informed consent form
IL-1	Interleukin-1
ISRs	injection site reactions
MWS	Muckle-Wells Syndrome
NOMID	Neonatal-onset Multisystem Inflammatory Disease
PASS	post authorization safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PRINTO	Pediatric Rheumatology International Trials Organisation
PSUR	periodic safety update report
RA	rheumatoid arthritis
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	summary of product characteristics
Sobi	Swedish Orphan Biovitrum

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Contact details of all Investigators participating in the study will be kept in a stand-alone document listed in Annex 1.

4 Abstract

Title	A non-interventional, post authorization safety study (PASS) to evaluate the safety of Kineret in the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in routine clinical care with regard to serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including re-use of syringe. Protocol version date: 10 June 2014 Main author: Kristine Bäck, Swedish Orphan Biovitrum
Rationale and background	CAPS is an ultra-rare disease which leads to overproduction of interleukin-1β and generates a life-long autoinflammatory syndrome. Kineret® is a human interleukin-1 (IL-1) receptor antagonist that has been approved for treating signs and symptoms of rheumatoid arthritis for more than 10 years. In November 2013 the European Commission approved Kineret in adult and pediatric patients for the treatment of CAPS, including Neonatal-onset Multisystem Inflammatory Disease (NOMID)/ Chronic Infantile Neurological Cutaneous Articular syndrome (CINCA), Muckle-Wells Syndrome (MWS) and Familial Cold Autoinflammatory Syndrome (FCAS). To meet the demands of administering lower and varying doses to pediatric CAPS patients, a new graduated syringe is being introduced to allow for single-use injections of doses in the interval 20-100 mg in steps of 10 mg. This non-interventional PASS is designed to address the effectiveness of the risk minimization measures for medication errors, including re-use of syringe. The study also addresses the pre-specified risks from the Risk Management Plan which can be captured at the patients' routine visits to the clinic (i.e. serious infections, malignancies, injection site reactions (ISRs) and allergic reactions). The Pediatric Rheumatology International Trials Organisation (PRINTO) network is a member of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The Eurofever registry, maintained by PRINTO, is a registry collecting data from patients with autoinflammatory diseases including patients with CAPS. As agreed with European Medicines Agency (EMA), this study is being set-up in collaboration with the PRINTO network.
Research question and objectives	The primary objective of the study is to evaluate the safety of Kineret treatment in CAPS patients in routine clinical care with focus on serious infections, malignancies, ISRs, allergic reactions and medication errors, including re-use of the syringe. Secondary objectives of the study are to evaluate the Kineret dosage over time, the proportions of patients who discontinue Kineret treatment temporarily or permanently and the proportion of patients who are transferred to another IL-1 blocking treatment.

Study design	This is a multicenter, non-interventional, non-controlled PASS to collect prospective data of CAPS patients treated with Kineret in routine clinical care. Data will be collected from patients receiving Kineret using the graduated syringe after market authorization. The planned duration of the follow-up period for each patient will be 3 years. In case the patient discontinues the Kineret treatment prematurely before 3 years, the data collection will be discontinued. Data will be captured at least once every year. However, Investigators will be encouraged to collect data at 6 month intervals if the patient has routine visits more frequently than once a year. At the first time point of data capture, the following Baseline data will be collected: • Visit date • Date of informed consent • Gender • Date of birth • Race • CAPS subtype (FCAS, MWS or NOMID/CINCA, or combination of subtypes) • Date of onset of CAPS symptoms • Date of CAPS diagnosis • Date of initiation of Kineret treatment • Date of initiation of Kineret treatment with graduated syringe • Kineret dose administered (mg/day) and body weight • History of other IL-1 blocking treatment • History of malignancies The following data will be collected at each post-Baseline visit: • Visit date • Occurrence of adverse events (AEs) related to serious infections, malignancies, ISRs and allergic reactions • Medication errors, including re-use of the syringe • Kineret dose administered (mg/day) and body weight • Start and stop date of any temporary discontinuation of Kineret treatment • Start date for permanent discontinuation of Kineret treatment • Reason for temporary or permanent discontinuation of Kineret treatment, including but not limited to, any AE leading to treatment discontinuation. • Transfer to any another IL-1 blocking treatment at discontinuation of Kineret treatment All other AEs spontaneously reported during the study will be reported through routine pharmacovigilance procedures.

Population	European CAPS patients treated with Kineret at the time of market authorization or starting treatment during the study enrollment will be eligible for inclusion in the study. The patients will be enrolled according to the treatment recommendations in the Summary of Product Characteristics. The patient and/or caregiver must give their consent to the study data collection. Study sites have been identified by PRINTO utilizing the Eurofever registry. The study is planned to start in UK, France and the Netherlands with possibility to add countries later (e.g. Italy).
Variables	The primary endpoints of the study are: • Rate of serious infections • Rate of new malignancies • Rate of ISRs • Rate of allergic reactions • Rate of medication errors including re-use of syringe Medication errors will be further classified as infections of the injection site, re-use of syringe, over- or underdosing, or other medication errors. The secondary endpoints of the study are: • Kineret dose (mg/kg/day) at Baseline and at year 1, 2 and 3 • Proportion of patients who discontinue Kineret treatment permanently including the reasons for the permanent discontinuations • Proportion of patients who discontinue Kineret treatment temporarily including the reasons for the temporary discontinuations • Proportion of patients who are transferred to another IL-1 blocking treatment
Data sources	The PRINTO network will organize the data collection. The source for all data will be the patients' medical records. The Investigators will verify the transfer of relevant prospective data to the electronic Case Report Form designed for the study in a web-based data entry tool.
Study size	All CAPS patients treated at the selected sites and meeting the inclusion criteria will be eligible for entry. The duration of the enrollment period will be 1 year and the study is estimated to enroll 15-20 CAPS patients. Based on study 03-AR-0298, it is estimated that the rate of both serious infections and ISRs is 0.08 events per patient year. Using Poisson distribution, the 95% confidence interval for an annual rate of 0.08 will be [0.02 – 0.19] in the case of 20 patients enrolled (equal to 44 patient years assuming a yearly drop-out rate of 20%). In the case of 15 enrolled patients (equal to 36.6 patient years), the 95% confidence interval will be [0.01 – 0.22].

Data analysis	The presence of serious infections, new malignancies, ISRs, allergic reactions and medication errors will be presented as rates, calculated as the number of events divided by the total cumulative exposure to Kineret treatment in the study (patient years). 95% confidence intervals will be calculated for the rate of each of the five event types. In addition to the rate, the distribution of the severity, relationship to the Kineret treatment and seriousness will be presented. All enrolled patients will be included in the analysis. The analyses will be conducted primarily for the total study population. In addition, the subgroup of patients who are already using Kineret at Baseline and the subgroup who initiate Kineret treatment at Baseline will be analyzed separately.
Milestones	The study is planned to start enrolling in October 2014 and end enrolling in October 2015. The data collection is planned to end in October 2018 with a final report prepared in June 2019. Safety data from the study will be reported yearly by Swedish Orphan Biovitrum to EMA and as part of the Kineret periodic safety update reports during the study period.

5 Amendments and updates

None

6 Milestones

Milestone	Planned date
Start of data collection	October 2014
End of enrollment (1 year)	October 2015
End of data collection	October 2018
Study progress report 1	Data lock point 01 May 2015
Study progress report 2 in connection with Periodic Safety Update Report (PSUR)	Data lock point 01 May 2016
Study progress report 3	Data lock point 01 May 2017
Study progress report 4	Data lock point 01 May 2018
Final report of study results in connection with PSUR	June 2019

7 Rationale and background

Cryopyrin Associated Periodic Syndromes

Cryopyrin Associated Periodic Syndromes (CAPS) is an ultra-rare, monogenic disease, caused by an autosomal dominant mutation in the *CIAS1* gene, which leads to overproduction of interleukin-1β, and generates a life-long autoinflammatory syndrome. CAPS include three subdiagnoses ranging from the milder manifestations of Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) to the clinically most severe form Chronic Infantile Neurological Cutaneous Articular syndrome (CINCA), also called Neonatal-Onset Multisystem inflammatory Disease (NOMID) in the US [1]. The estimated prevalence of CAPS is 1-9 in 1 000 000 [2].

CAPS is characterized by variable degrees of inflammatory symptoms, including persistent urticarial-like skin rash, arthralgia, fever, headache, malaise and hearing loss. Severe neurological involvement, with brain atrophy, mental retardation, and bone dysplasia only occurs in the most severe form, NOMID/CINCA.

Kineret® (anakinra)

Kineret is a human interleukin-1 (IL-1) receptor antagonist (r-metHuIL-1ra) produced in *Escherichia coli* cells by recombinant DNA technology. Kineret was approved for treating signs and symptoms of rheumatoid arthritis (RA) in adults by US Food and Drug Administration (FDA) in 2001 and by the European Commission in 2002. In December 2012, the FDA approved Kineret for the treatment of children and adults with NOMID/CINCA, the most severe form of

CAPS. In November 2013 the European Commmission approved Kineret in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above, for the treatment of CAPS, including NOMID/CINCA, MWS and FCAS.

The application for a new indication for the treatment of CAPS was based on the pivotal clinical study 03-AR-0298. Study 03-AR-0298 was an Investigator-sponsored, open-label study, conducted at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, USA. The study included 43 patients treated with Kineret for up to 5 years (total Kineret exposure of 159.8 patient years). Of the 43 patients included, 36 were diagnosed with NOMID/CINCA and 7 patients had characteristics overlapping between MWS and NOMID/CINCA.

If not specifically stated, the below described adverse events (AEs) and safety in RA refers to data from a safety data pool consisting of 5 major placebo-controlled, randomized, blinded clinical studies in patients with RA older than 18 years. The safety pool includes in total 2372 RA patients treated with Kineret and 958 treated with placebo for up to 6 months. Open label safety studies, studies in healthy volunteers, indications other than RA, and studies where Kineret treatment was used in combination with other treatments (except methotrexate) are not included in the RA safety pool.

Risk minimization for medication errors; ready for use graduated prefilled syringe

To meet the demands for use in children with CAPS that need smaller and varying doses of Kineret, a new pre-filled syringe is currently being introduced. The syringe is supplied with a graduated label to allow for single-use injections of doses in the interval 20-100 mg in steps of 10 mg. For a 100 mg dose, all the content of the syringe is injected. For doses between 20-90 mg, excess of Kineret is discarded onto a sterile gauze or tissue before injection. When the plunger front has reached the scale mark of the Kineret dose, the syringe is ready for injection.

There is a potential risk of overdosing or underdosing if the wrong volume of Kineret is injected. To minimize the likelihood of medication errors associated with Kineret therapy, carefully designed instructions for use are provided in the package leaflet.

Educational materials has also been made available to both healthcare providers and patients/caregivers before the launch of the graduated syringe. The healthcare provider should instruct the patient and caregiver on how to correctly inject the prescribed dose and dispose of used syringes.

A usability study with the graduated syringe was conducted as a pre-approval activity in the US letting adult caregivers handle water-filled graduated syringes and inject into an injection pad (i.e. not into the body). The study demonstrated that the Kineret graduated syringe can be handled safely and effectively by first time users after one training session (held by their healthcare provider) with the help of the instructions for use. The usability study results have also been reported to the European Medicines Agency (EMA) as part of the Extension Application for Kineret for the addition of a new indication and strength [3].

Injection Site Reactions

The most frequently reported adverse reactions with Kineret in placebo-controlled studies in RA patients were Injection Site Reactions (ISRs) and ISRs were the most common reason for

withdrawal from study in Kineret-treated RA patients. The frequency of ISRs in CAPS patients in study 03-AR-0298 was similar to the frequency of ISRs in the placebo group in the RA studies and there were no permanent or temporary withdrawals of Kineret due to ISRs in CAPS patients. ISRs typically appear within 2 weeks' therapy and disappear within 4-6 weeks. The development of ISRs in patients who have not previously experienced ISRs was uncommon after the first month of therapy.

All healthcare providers treating CAPS patients with Kineret should instruct the patient/caregiver on how to avoid discomfort at the site of the injection and alleviate the signs and symptoms of ISRs, as described in the Summary of Product Characteristics (SmPC) [4] and educational materials for healthcare providers and patients/caregivers.

Serious infections

An increased susceptibility to infections is a potential safety issue with an agent that alters cytokine response. Kineret has been associated with an increased incidence of serious infections (1.8%) vs. placebo (0.7%) [4]. For a small number of patients in RA studies with asthma, the incidence of serious infection was higher in Kineret-treated patients (4.5%) vs placebo-treated patients (0%), these infections were mainly related to the respiratory tract. The safety and efficacy of Kineret in patients with chronic infections have not been evaluated. In clinical studies, concurrent administration of Kineret and etanercept in RA patients has been associated with an increased risk of serious infections. It is reasonable to assume that this interaction is valid not just for etanercept but for the whole class of Tumor Necrosis Factor alpha (TNF-α) antagonists and that the results of the RA studies above apply also to CAPS patients.

Re-use of a syringe may cause infections. It is not possible to estimate the magnitude of the infection risk since it depends on multiple factors, e.g. injection technique, cleaning of injection site, and time of storage in room temperature. Most infections will likely be mild and local at the injection site. There is, however, a risk for serious infections, mainly bacteremias and sepsis.

Malignancies

No overall increased frequency of malignancies in Kineret-treated patients has been observed in clinical studies in RA, including long-term follow-up data. In CAPS study 03-AR-0298, there were no adverse reactions denoting malignancies. The impact of treatment with Kineret on pre-existing malignancies has not been studied, therefore the use of Kineret in patients with a pre-existing malignancy is not recommended. Due to the immunosuppressive properties of Kineret there is a theoretical risk that Kineret could increase the frequency of malignancies.

Allergic reactions

In clinical studies in RA patients the frequency of allergic reactions was approximately 3% higher for Kineret-treated patients compared to placebo, including all kinds of allergic reactions, e.g. seasonal allergy and hay fever. In study 03-AR-0298 23 of 43 CAPS patients had at least one AE related to allergic reactions. 75% of those events included rash, ocular hyperemia and urticaria that also are representing common symptoms of NOMID/CINCA. No event required discontinuation of Kineret treatment.

Study rationale

This non-interventional post authorization safety study (PASS) was included in Section III.4.3 of the Risk Management Plan (RMP) as a category 3 activity. The study is designed to address the effectiveness of the risk minimization measures for medication errors, including re-use of syringe. The study also addresses the pre-specified risks from the RMP which can be captured at the patients' routine visits to the clinic (i.e. serious infections, malignancies, ISRs and allergic reactions). Risks which would require specific assessment have not been included as endpoints in this study.

Eurofever registry

As agreed with EMA, this PASS will utilize the Eurofever registry to find and prospectively follow the CAPS patients post authorization. Eurofever is an international registry for autoinflammatory diseases and the Eurofever project was promoted by the Autoinflammatory Diseases' Working Group of the Pediatric Rheumatology European Society and by the Pediatric Rheumatology International Trials Organisation (PRINTO at www.printo.it) and has been supported by the Executive Agency for Health and Consumers [5]. Eurofever is organized and maintained by PRINTO. The PRINTO network is a member of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

In September 2013, Eurofever had 2835 patients enrolled in total, among them 225 with CAPS [6]. In a recent extended report about treatment of autoinflammatory diseases, the first 94 patients with CAPS enrolled in the Eurofever registry were analyzed; anakinra was used in a total of 82 patients [7].

Study protocol and reporting of data

The protocol for this study has been developed in accordance with the guidance for the format and content of the protocol of a non-interventional PASS [8]. The protocol will be published in the EU PAS register. The collected safety data and the study progress will be reported to EMA Pharmacovigilance Risk Assessment Committee (PRAC) in the yearly study progress reports, in connection with planned PSURs and in RMP updates where applicable.

8 Research question and objectives

The primary objective of the study is to evaluate the safety of Kineret treatment in CAPS patients in routine clinical care with focus on serious infections, malignancies, ISRs, allergic reactions and medication errors, including re-use of the syringe.

Secondary objectives of the study are to evaluate the Kineret dosage over time, the proportions of patients who discontinue Kineret treatment temporarily or permanently and the proportion of patients who are transferred to another IL-1 blocking treatment.

9 Research methods

9.1 Study design

This is a multicenter, non-interventional, non-controlled PASS to collect prospective data in routine clinical care where CAPS patients are treated with the Kineret graduated syringe. The planned duration of the follow-up period for each patient will be 3 years. In case the patient discontinues the Kineret treatment prematurely before 3 years, the data collection will be discontinued (see below) and the patient will be withdrawn from the study. Data will be captured at least once every year. However, Investigators will be encouraged to collect data at 6 month intervals if the patient has routine visits more frequently than once a year.

If the patient permanently discontinues the Kineret treatment before the 3-year Visit, study data will be collected up to and including the last day of Kineret treatment. The recording of this data may, however, be performed at the next scheduled doctor's appointment/contact. The process and timelines for collection of AEs are described further in Section 11.2.

If the patient has a planned or spontaneous temporary discontinuation of Kineret treatment, the patient can stay in the study.

The recording of temporary and permanent discontinuations are described in Sections 9.1.1.5 and 9.1.1.6.

Other reasons for discontinuation/withdrawal of a patient from the study could be lost to follow-up, withdrawal of consent or incorrect enrollment, i.e. the subject did not meet the required eligibility criteria for the study at the time of inclusion.

9.1.1 Data capture

At the first time point of data capture, the following Baseline data will be collected:

- Visit date
- Date of informed consent by the patient and/or caregiver
- Gender
- Date of birth
- Race
- CAPS subtype (FCAS, MWS or NOMID/CINCA, or combination of subtypes)
- Date of onset of CAPS symptoms
- Date of CAPS diagnosis
- Date of initiation of Kineret treatment
- Date of initiation of Kineret treatment with graduated syringe
- Kineret dose administered (mg/day) and body weight

- History of other IL-1 blocking treatment
- History of malignancies

Date of birth, date of onset of CAPS symptoms and date of CAPS diagnosis will be used to calculate age, disease duration and time since onset of CAPS symptoms.

The following data will be collected at each post-Baseline visit:

- Visit date
- Occurrence of AEs related to serious infections, malignancies, ISRs and allergic reactions
- Medication errors, including re-use of the syringe
- Kineret dose administered (mg/day) and body weight
- Start and stop date of any temporary discontinuation of Kineret treatment
- Start date for permanent discontinuation of Kineret treatment
- Reason for temporary or permanent discontinuation of Kineret treatment, including but not limited to, any AE leading to treatment discontinuation.
- Transfer to any another IL-1 blocking treatment at discontinuation of Kineret treatment

9.1.1.1 Pre-specified adverse events

The following pre-specified AEs, both non-serious and serious, related and not related to Kineret, reported during the study period will be captured in the study database.

- Serious infections
- Malignancies
- ISRs
- Allergic reactions

Management and reporting of AEs are further described in Section 11.

9.1.1.2 Medication errors

Medication errors will be collected by asking about the presence of infections of the injection site, re-use of syringe, overdosing, underdosing or other medication errors since the previous recording. Other medications errors will be collected by asking the patient if they have had any other problems with using the syringe or administering the right dose. All medication errors will be reported as AEs, independent of outcome.

9.1.1.3 Kineret dose

To calculate the Kineret dose in mg/kg/day, the Kineret dose (mg/day) will be recorded at Baseline and on visits at year 1, 2 and 3 (and if applicable, at 6 months interval visits and/or at the time of permanent discontinuation of Kineret treatment).

9.1.1.4 Body weight

The body weight will be recorded at Baseline and on isits at year 1, 2 and 3 (and if applicable, at 6 months interval visits and/or at the time of permanent discontinuation of Kineret treatment). Body weight will be used to calculate the administered Kineret dose in mg/kg/day.

9.1.1.5 Permanent discontinuation of Kineret treatment

Permanent discontinuation of Kineret treatment will be recorded, including the reasons for the permanent discontinuation and the date of the last dose taken. The primary reason for the treatment discontinuation will be classified as one of the following:

- AE (to be specified)
- Other reason (to be specified).

In case the primary reason for the treatment discontinuation is an AE, the AE will be recorded in the study database, even if it is not one of the pre-specified AEs in Section 9.1.1.1.

Patients registered as having permanently discontinued Kineret treatment should not re-enter the study even if the Kineret treatment is re-instituted.

9.1.1.6 Temporary discontinuation of Kineret treatment

Temporary discontinuation of Kineret treatment will be recorded, including the reasons for the temporary discontinuation and the start date of the temporary discontinuation. In addition, the date of the re-institution of the Kineret treatment will be recorded. The primary reason for the temporary treatment discontinuation will be classified as one of the following:

- AE (to be specified)
- Other reason (to be specified)

In case the primary reason for the temporary treatment discontinuation is an AE, the AE will be recorded in the study database, even if it is not one of the pre-specified AEs in Section 9.1.1.1.

9.1.1.7 Patients transferred to another IL-1 blocking treatment

If the patient is transferred to another IL-1 blocking treatment after the discontinuation of the Kineret treatment, the IL-1 blocking treatment will be recorded together with the date of the discontinuation The IL-1 blocking treatment will be classified as one of the following:

- canakinumab
- other IL-1 blocking treatment (to be specified)

9.2 Setting

Patients will be enrolled according to the approved treatment recommendation for CAPS in the SmPC [4]. If the patient receives Kineret outside of the approved treatment recommendations for CAPS (e.g. patient treated despite contraindication) the patient should not be enrolled in this

study. CAPS patients eligible for inclusion in the study will either already be using the Kineret graduated syringe or just about to start Kineret treatment with the graduated syringe.

The study inclusion criteria that applies at enrollment are:

1) Informed consent by the patient and/or caregiver
2) Kineret treatment will be according to the SmPC, as confirmed by the Investigator

No specific exclusion criteria will be applied. Hence the study population will be representative of the population of CAPS patients treated in in routine clinical care.

Clinical sites and Investigators treating CAPS pediatric and adult patients have been identified via the Eurofever registry, organized and maintained by PRINTO. By September 2013, 225 CAPS patients had been enrolled in the Eurofever registry [6]. The site feasibility was done by PRINTO by asking a number of Investigators in the Eurofever registry for their interest and capability to recruit patients in this non-interventional PASS.

The selection of participating countries, clinical sites and Investigators has been based on;

- Availability of the Kineret graduated syringe (Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe) during the period of study enrollment
- Location of larger clinical sites treating CAPS patients with Kineret

The study will include both pediatric and adult patients. Kineret is approved for treating patients with CAPS aged 8 months and older (with a body weight of 10 kg or above).

9.3 Variables

9.3.1 Primary endpoints

The primary endpoints of the study are:

- Rate of serious infections
- Rate of new malignancies
- Rate of ISRs
- Rate of allergic reactions
- Rate of medication errors including re-use of syringe

Medication errors will be further classified as infections of the injection site, re-use of syringe, over- or underdosing, or other medication errors.

The rates will be calculated for events which are treatment-emergent, defined as events which start after the date of the first dose of Kineret using the graduated syringe and after the date of informed consent (i.e., after the later of the two dates). The events which start after the Kineret treatment has been terminated, start during a temporary discontinuation of Kineret treatment or after the completion of the study will not be included for the calculation of the rates.

The rates will be calculated as the number of events divided by the total cumulative exposure to Kineret treatment in the study (patient years). The cumulative exposure to the Kineret treatment will be calculated for the period corresponding to the evaluation period of the treatment-emergent AEs, i.e. from the date of the first dose of Kineret using the graduated syringe or date of informed consent (later of the two dates) until the date of temporary discontinuation of the Kineret treatment or study completion (first of the two dates). The period during which Kineret treatment has been temporarily discontinued will be excluded from the cumulative exposure.

9.3.2 Secondary endpoints

The secondary endpoints of the study are:

- Kineret dose (mg/kg/day) at Baseline and at year 1, 2 and 3
- Proportion of patients who discontinue Kineret treatment permanently including the reasons for the permanent discontinuations
- Proportion of patients who discontinue Kineret treatment temporarily including the reasons for the temporary discontinuations
- Proportion of patients who are transferred to another IL-1 blocking treatment

9.4 Data sources

The PRINTO network will organize the data collection. The source for all data will be the patients' medical records. The Investigators will verify the transfer of relevant prospective data to the electronic case report form (eCRF) designed for the study in a web-based data entry tool.

English will be the official language used for all forms completed by the Investigators.

9.5 Study size

All CAPS patients treated at the selected sites and meeting the inclusion criteria will be eligible for entry. The duration of the enrollment period will be 1 year and the study is estimated to enroll 15-20 CAPS patients.

Based on study 03-AR-0298, it is estimated that the rate of both serious infections and ISRs is 0.08 events per patient year. Using Poisson distribution, the 95% confidence interval for an annual rate of 0.08 will be [0.02 – 0. 19] in the case of 20 patients enrolled (equal to 44 patient years assuming a yearly drop-out rate of 20%). In the case of 15 enrolled patients (equal to 36.6 patient years), the 95% confidence interval will be [0.01 – 0.22].

9.6 Data management

Data will be collected on-line via the secured PRINTO website on a dedicated server. Technical management of the database will be handled by PRINTO. The web system is accessible only to

authorized personnel through unique individual usernames and passwords to allow record traceability. The completed eCRFs are the sole property of Istituto Gaslini and should not be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities, Ethics Committees (ECs) and if applicable a monitor appointed by Swedish Orphan Biovitrum (Sobi). Investigators' access to the eCRFs is restricted to the patients under their care.

Data will be cleaned and remotely monitored by PRINTO on an ongoing basis to check the accuracy of data. If necessary, The PRINTO will ask the site of additional or more precise information.

The data management process will be documented in the data management plan (DMP).

9.7 Data analysis

Main summary measures

The presence of serious infections, new malignancies, ISRs, allergic reactions and medications errors will be presented as rates, calculated as the number of events divided by the total cumulative exposure to Kineret treatment in the study (patient years). 95% confidence intervals will be calculated for the rate of each of the five event types. In addition to the rate, the distribution of the severity, relationship to Kineret treatment and seriousness will be presented.

Main statistical methods

All enrolled patients will be included in the analysis. The analyses will be conducted primarily for the total study population. In addition, the subgroup of patients who are already using Kineret at Baseline and the subgroup who initiate Kineret treatment at Baseline will be analyzed separately. In the primary analyses, the analysis period will cover the time from Baseline visit until the last visit. For the rate of malignancies, a secondary analysis will be conducted by including the time from the initiation of Kineret treatment until the last study visit.

All endpoints will be summarized using 95% confidence intervals and descriptive statistics. No formal statistical comparison will be done.

Missing values

For incompletely recorded dates, a missing day is replaced by 15 and a missing month by 6. However, in case of missing data on the data of onset of an AE, if it is not obvious whether the AE is treatment-emergent or not, the AE will be classified as treatment-emergent.

Sensitivity analyses

No sensitivity analyses have been planned for this study.

Amendments to the Statistical Analysis Plan

A separate statistical analysis plan (SAP) will be written for this study. The first version of the SAP is this section (Section 9.7) of the protocol. The second version will be finalized before the start of the study. The plan will be updated on an as-needed basis during the study. The purpose of the second version of the SAP is to describe the main summary measures and the main

statistical methods in more detail and to describe the outputs generated from the data. The plan will be written in collaboration between PRINTO and Sobi.

9.8 Quality control

Collection of data will follow the routine clinical care in treatment of the patients. The source for all collected data will be the patients' medical records. It is the responsibility of the Investigator to ensure completion and to review and approve all eCRFs. At all times, the Investigator has the final responsibility for the accuracy and authenticity of all patient data entered into the eCRFs.

The web system is provided with validation control and it is not expected to have missing data related to mandatory questions. However, all the data entered into the web system will be reviewed by the PRINTO Coordinating Centre for completeness and accuracy. PRINTO personnel will check the completeness and coherence of the data; if any relevant query is raised during the check, PRINTO will contact the Investigator to: verify the correctness and consistency of the data and retrieve missing data if available. In case of discrepancies, specific queries will be issued and solved through the Query Ticket system. Data can be updated or modified only upon request to the PRINTO helpdesk.

Issues that arise and that are not possible to resolve within the entry tool may be managed by a site review. Data will be validated on an ongoing basis, and, a specific validation process will be applied.

All validation of data will be described in detail in the DMP.

9.9 Limitations of the research methods

This PASS is designed to address the effectiveness of risk minimization measures for medication errors, including re-use of syringe with potential infection risk of the injection site, and over- or underdosing. The study will also address the pre-specified risks from the RMP which can be captured at the patients' routine visits to the clinic (i.e. serious infections, malignancies, injection site reactions and allergic reactions). Risks which would require specific assessment have not been included as endpoints in this study.

An uncontrolled study design is deemed acceptable for this non-interventional PASS which aims to assess the risk minimization measures specific to Kineret treatment listed above. Accordingly, the study design carries the general limitations inherent in an uncontrolled design regarding statistical analyses, interpretation, generalizability and conclusiveness.

Since CAPS is an ultra-rare disease the size of the population limits the number of patients to be included in the study. Previous use of the Kineret graduated syringe will not be an exclusion criterion at enrollment. Therefore the study may not, for all patients enrolled, capture medication from the patient's first time use of the graduated syringe.

9.10 Other aspects

All aspects of the research method have been covered in the other sections of the study protocol.

10 Protection of human subjects

10.1 Conduct of study

This study will comply with the definition of a non-interventional PASS and will be conducted in compliance with the clinical study protocol, the Guideline of Good Pharmacovigilance Practices (GVP) Module VIII – Post Authorisation Safety Studies [9] and Guidelines for Good Pharmacoepidemiological Practices (GPP) [10] and applicable regulatory/governmental regulations.

The study will follow the ethical principles in the latest revision of the Declaration of Helsinki for Medical Research Involving Human Subjects [11] and will comply with applicable local ethical requirements for each included clinical site.

The personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). The Investigator will also ensure that this study is conducted in accordance with the laws and regulations of the country in which the research is conducted.

10.2 Pharmacovigilance Risk Assessment Committee review

The Study Synopsis has been agreed with PRAC as part of the RMP and the study protocol will be transmitted by Sobi to PRAC and all EU Member States via notification from the EU electronic register of post-authorization studies (EU PAS register) and according to national procedures, as applicable. Sobi will make study information available in the EU PAS register. The study protocol will be entered in the register before the start of data collection and updates to the study protocol in case of substantial amendments, progress reports, and the final study report will consequently be entered.

10.3 Ethics committee review

The Investigator (or national coordinator where applicable) is responsible for submitting this protocol, informed consent forms (ICF), and if any accompanying material to be provided to the patient (such as patient information sheets, or descriptions of the study used to obtain informed consent) to an EC, where applicable according to local regulations. The Investigator will not begin any study activities until approval from the EC has been documented and provided as a letter to the Investigator. If required, the national coordinating Investigator is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC. Investigators are also responsible for promptly informing the EC of any protocol amendments as applicable. Any subsequent changes to the EC submitted study documents, including amendments, will require resubmission and reapproval by the EC before implementation, with the exception of those necessary to reduce immediate risk to the patients. It is the responsibility of the Investigator to ensure that all interactions with EC are conducted in accordance with current governmental regulations.

10.4 Informed consent

It is the responsibility of the Investigator to give each patient (and/or the patient's representative) prior to any study-related activities, full and adequate verbal and written information in local language regarding the study, including aims, methods, objectives, study activities/procedures, the possible risks/hazards involved in participation, data protection, and alternatives of the study. The Investigator must utilize the most current Sobi and EC approved ICF for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by EC or local requirements. The medical record for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

Patients may decline the invitation and refuse consent without giving a reason and without prejudice to any treatment that is proposed. The patients must be informed about their right to withdraw from the study at any time.

The consent forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The written patient information and/or consent form must not be changed without prior agreement with Sobi. Before any revisions are implemented, the revised written patient information, consent and/or assent form must be approved by the EC.

10.5 Confidentiality

Patient identity information (i.e., first and last name, date of birth and the national patient unique identifier) will be available ONLY for authorized study site personnel that have entered the data by using a personal password together with a study site password. The PRINTO web system will automatically ENCRYPT the patient identity information and ONLY the encrypted data will be saved on the on the PRINTO central database on an https platform. The PRINTO website will automatically assign a PRINTO patient id number,to be used for communication with the study site.

The PRINTO encrypting algorithm is designed in a way by which it is impossible for PRINTO to decrypt the patient identity information. This means that patient identity information is not included in study data sets or any documentation that are transmitted to Sobi or submitted to EC, regulatory authority, or any third party. The study data sets will include information about age, disease duration and time since onset of CAPS symptoms, i.e. data that has been calculated from patient identity information.

Medical records and data collected during the study will not be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities, ECs and if applicable a monitor designated by PRINTO or Sobi.

10.6 De-identification of patient data

Patient data will be anonymized through design of data entry fields that do not permit the entry of identifying information such as study site-assigned patient identifiers. Only authorized study site personnel will enter data into eCRFs. The patient's identity information will be entered by the study site and encrypted as detailed in Section 10.5. No patient identifiers used by sites will be entered; rather patients will be assigned a study-specific identification number (ID). The anonymized data, as entered into the EDC system, will be visible to PRINTO and Sobi, but only authorized study site personnel will be able to trace a case ID back to a patient identity, a necessary measure to allow study site personnel to respond to data queries raised later. Detailed explanation of data protection and patient confidentiality measures will be included in each application for EC approval as applicable. Where necessary, these will include country-specific measures.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patients will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations. Only authorized study site personnel will have access to identifiable personal details, if required for data verification. The Investigator is responsible for retrieval of information from personal medical records.

In any presentations or in publications of the results of the study, the patient's identities will remain anonymous and confidential. If Sobi, its designee(s), and various government health agencies should inspect the records of the study, every effort will be made to keep the patient's personal medical data confidential. See more about publications in Section 12.

10.7 Sponsor documents

The Investigator agrees that all information received from Sobi, including but not limited to this clinical study protocol and any other study information remain the sole and exclusive property of Sobi during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Sobi. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.8 PRINTO documents

The eCRF and database, remain the sole and exclusive property of the Gaslini hospital during the conduct of the study and thereafter. Data will be exclusive property of the Gaslini hospital and will be shared with Sobi for the purpose of reporting to health authorities.

11 Management and reporting of adverse events/adverse reactions

11.1 Definitions

11.1.1 Adverse event

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

AEs include the following:

- Abnormal test findings, as specified below
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Progression/worsening of underlying disease
- Medication errors. Any medication error is reported as an AE, independent of outcome

In addition, signs and symptoms resulting from the following will also be handled according to the same principles as AEs:

- Overdose
- Abuse
- Misuse
- Lack of efficacy
- Pregnancy and breast feeding (see Section 11.3)

11.1.2 Serious adverse event

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death
- Is life-threatening (i.e., at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study patient)

Other medically important AEs that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. 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 dependency or abuse.

Serious also includes any other event judged by investigator or company as serious.

11.2 Eliciting and recording adverse event information

11.2.1 Pre-specified adverse events

The following pre-specified AEs, both non-serious and serious, related and not related to Kineret, reported during the study period will be captured in the study database:

- Serious infections
- New malignancies
- ISRs
- Allergic reactions

For patients who have already used the Kineret graduated syringe before enrollment into the study, pre-specified non-serious AEs will be collected from when the patient has signed the ICF until the last Year 3 data entry. For patients who have not used the Kineret graduated syringe previously, the pre-specified non-serious AEs will be collected from the first day that the patient use the Kineret graduated syringe after ICF until the last Year 3 data entry. For patients who permanently discontinue Kineret treatment before the Year 3 data entry, any pre-specified non-serious AEs occurring within 3 days after the last dose will be collected (for serious AEs see paragraph 11.2.3).

The Investigator is to record the occurrence of any of the pre-specified AEs above, on the eCRF. For the pre-specified AEs, the reported AE term, onset, frequency, severity, relationship to Kineret, seriousness, action taken regarding the Kineret treatment and resolution (when available) will be collected.

11.2.2 Other non-serious adverse events

All other non-serious AEs (i.e. AEs not specified in Section 11.2.1) spontaneously reported will be reported through routine pharmacovigilance procedures and not via the eCRF.

11.2.3 Serious adverse events

Patients on “Kineret non-graduated syringe” since before may have a routine visit to their healthcare provider where informed consent is collected before they start using the Kineret graduated syringe. Serious adverse events (SAEs) will be collected from the time of informed consent until the last Year 3 data entry. For patients who permanently discontinue Kineret treatment, any SAE will be collected up to 1 month after the last dose.

All SAEs will be entered in the study database and the safety database and will acquire reconciliation.

For each SAE and pre-specified non-Serious AE, the Investigator will be requested to make a causality assessment to determine if there is a reasonable possibility that Kineret caused the AE, i.e., if the AE is assessed as related or not related to Kineret. An SAE assessed as related to Kineret is to be considered an adverse reaction.

Concomitant medication will only be recorded as part of an SAE reporting or spontaneous AE reporting and will be entered in the safety database and not be a part of the study database.

When an SAE is identified, it shall be reported via sending the AE report to Sobi (fax number +46 8 697 32 30 or email drugsafety@sobi.com) and by completion of the AE report in the eCRF, within 24 hours of awareness by the Investigator.

11.3 Exposure during pregnancy or via breastfeeding

All events of exposure to Kineret during pregnancy (female patient or male patient's partner) or via breastfeeding shall be reported to Sobi and entered into the eCRF system within 24 hours of awareness by any study personnel. Pregnancies shall be reported regardless of whether the exposure is associated with an AE or not. This includes all situations where a female is or has been found to be pregnant after being exposed to Kineret; directly, indirectly or via her partner (paternal exposure).

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy Report Form which shall be completed and returned by the investigator. The investigator is responsible for monitoring the outcome of the pregnancy and to inform Sobi of relevant information and any information requested related to the outcome of the pregnancy.

11.4 Follow-up of unresolved adverse events

All AEs should be followed until they are resolved or the investigator assesses them as chronic or stable, or the patient's participation in the study ends. In addition, all serious and non-serious AEs assessed by the investigator as related to Kineret should continue to be followed until they resolve or until the investigator assesses them as "chronic" or "stable", even after the patient's participation in the study is over.

11.5 Monitoring of the benefit-risk balance

Sobi Drug Safety will regularly review all reported AEs and other safety data collected for the product, within the study and from any other sources. If any significant new safety information relevant for the treatment of the patients in the study is identified, including any changes in benefit risk balance, Sobi will assess the potential impact on the study protocol and a communication will be issued to all Investigators.

12 Plans for disseminating and communicating study results

Safety data collected while the study is ongoing will be communicated in the yearly study progress reports, in connection with planned PSURs and RMP updates as described in Section 6. A final report of study results is planned to be compiled at the end of the study in connection with next planned PSUR.

After completion of the study, the study data may be considered for reporting at a scientific meeting or for publication in a scientific journal according to the PRINTO publication policy [12]. Sobi has the rights to review and comment on the content and timelines of any publication before submission, concerning disclosure of any confidential information and Intellectual Property purposes related to Kineret. Decision to publish will be the responsibility of PRINTO according to the PRINTO publication policy.

Sobi will publicly register this study in the EU PAS register and on www.clinicaltrials.gov.

13 References

1 Goldbach-Mansky R.. Current status of understanding the pathogenesis and management of patients with NOMID/CINCA. Curr Rheumatol Rep. 2011;3(2):123-31.

2 Orphanet: information about Cryopyrin associated periodic syndrome updated March 2014, available from www.orpha.net

3 Assessment Report for Kineret by Committee for Medicinal Products for Human Use (CHMP) 19 September 2013. EMA/CHMP/398765/2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000363/WC500156808.pdf

4 Summary of Product Characteristics Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000363/WC500042310.pdf (page 10-21)

5 Executive Agency for Health and Consumers (EAHC) Project no 2007332, available from http://ec.europa.eu/eahc/projects/database.html

6 PRINTO Newsletters No 20 – September 2013 available from https://www.printo.it/newsletters.asp

7 ter Haar N et al. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. Ann Rheum Dis 2013;72:678-85.

8 EMA Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies, current version dated 26 September 2012.

9 EMA Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies, current version dated 15 April 2014.

10 Guidelines for Good Pharmacoepidemiological Practices (GPP), Current version published online 2007. Available from: http://www.pharmacoepi.org/resources/ispe_guidelines_2008.pdf

11 World Medical Association Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, latest amendment at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Available from: http://www.wma.net/en/30publications/10policies/b3/

12 Pediatric Rheumatology International Trials Organization (PRINTO) and of the Pediatric Rheumatology Collaborative Study Group (PRCSG) authorship and publication policy available from https://www.printo.it/paper-publication-guidelines.asp

Annex 1. List of stand-alone documents

Number	Date	Title
1	15 August 2013	Risk Management Plan
2	To be finalized at the time of the start of data collection.	Data Management Plan
3	The second version will be finalized at the time of the start of data collection.	Statistical Analysis Plan
4	27 June 2014	Master adult Patient Information sheet and Informed Consent Form
5	27 June 2014	Master Parent Information sheet and Informed Consent Form
6	27 June 2014	Master minor Patient Information and Informed Consent/Assent Form
7	First version to be finalized at the time of the start of data collection.	Contact details and list of national coordinating Investigators and Investigators of participating sites

Annex 2. ENCePP checklist for study protocols