Name of Company: Swedish Orphan Biovitrum Name of Finished Product: Kineret Name of Active Ingredient: anakinra	Individual Study Table	(For National Authority Use Only)

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.

Keywords

Kineret, Anakinra, PASS, graduate syringe, CAPS

Rationale and background

CAPS is an ultra-rare, monogenic autoinflammatory disease, caused by autosomal dominant mutation of the *NLRP3 (CIAS1)* gene, which leads to overproduction of interleukin (IL)-1β. Patients with CAPS can present various symptoms, historically classified in three disorders: Familial Cold Auto inflammatory Syndrome (FCAS), Muckle-Wells syndrome (MWS) and Chronic Infantile Neutrophilic Cutaneous Articular Syndrome/ Neonatal Onset Multisystem Inflammatory Disorder (CINCA/NOMID). However, these disorders are now recognized as a severity spectrum rather than separate entities (1, 2).

Kineret is a human IL-1 receptor antagonist (r-metHuIL-1ra) produced by Escherichia coli cells treated with recombinant DNA technology. Kineret was first approved for treating signs and symptoms of rheumatoid arthritis (RA) in adults by 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 manifestation of CAPS. In November 2013, the European Commission 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 new indications of Kineret in CAPS patients from 2012 were based on the pivotal clinical study 03-AR-0298. The 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, US. 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.

The safety profile of anakinra is well known. The risks identified in the risk management plan (RMP) are mainly based on safety data pool consisting of 5 major placebo-controlled, randomized, blinded clinical studies in patients with RA older than 18 years. The safety data pool includes a total of 2372 RA patients treated with Kineret and other 958 treated with placebo for up to 6 months.

To meet the demands for using Kineret in CAPS children needing smaller and varying doses, a pre-filled syringe was introduced. The graduated syringe was available on the US market in August 2013 and in the first European country (UK) in April 2014.

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

In addition, educational materials were made available to both healthcare providers and patients/caregivers before the launch of the graduated syringe, as a risk minimization measure. The healthcare provider should instruct the patient and the caregiver on how correctly injecting the prescribed dose and disposing of used syringes.

In agreement with European Medicines Agency (EMA) a non-interventional PASS was included in Section III.4.3 of the RMP (Additional pharmacovigilance activities) as a category 3 activity. The final RMP version agreed with EMA at the time was version 3.2, dated 2013-09-13. The study was designed to address the effectiveness of the risk minimization measures for medication errors, including re-use of a syringe. The study also addressed 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 of this study.

This PASS has utilized the Eurofever registry to find and prospectively follow the CAPS patients post Kineret 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 PRINTO network (at www.printo.it) and has been supported by the Executive Agency for Health and Consumers. Eurofever is organized and maintained by PRINTO. The PRINTO network is a member of the ENCePP.

Research question and objectives

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

The secondary objectives of the study were 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 was a multicenter, non-interventional, non-controlled PASS to collect prospective data in routine clinical care where CAPS patients were treated with the graduated syringe of Kineret. The duration of the follow-up for each patient was planned to be 3 years. In case the patient discontinued the Kineret treatment prematurely before 3 years, the data collection was to be discontinued (see below) and the patient was to be withdrawn from the study. Data was captured

at least once every year. However, Investigators were encouraged to collect data at 6 months intervals if the patient has routine visits more frequently than once a year.

If the patient permanently discontinued the Kineret treatment before the 3-year visit, study data was to be collected up to and including the last day of Kineret treatment. However, the recording of this data could be performed at the next scheduled doctor's appointment/contact.

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

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

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

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

Setting

Patients were enrolled according to the approved treatment recommendation for CAPS in the summary of product characteristics (SmPC, Section 4.1, Therapeutic indications and 4.2 Posology and method of administration). If the patient received Kineret outside of the approved treatment recommendations for CAPS (e.g. patient treated despite contraindication), the patient was not to be enrolled in this study. CAPS patients eligible for inclusion in the study could either already be using the Kineret graduated syringe or just about to start Kineret treatment with the graduated syringe.

The study inclusion criteria applied at enrollment were:

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

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

Subjects and study size, including dropouts

Clinical sites and investigators treating CAPS pediatric and adult patients were identified via the Eurofever registry. By September 2013, 225 CAPS patients had been enrolled in the Eurofever registry (3).The site feasibility was done by Pediatric Rheumatology International Trials Organisation (PRINTO) by asking a number of investigators in the Eurofever registry for their interest and capability to recruit patients in this non-interventional PASS.

All CAPS patients treated with Kineret at the selected sites and meeting the inclusion criteria were eligible for entry.

The planned duration of the enrollment period was 1 year and the study was estimated to enroll 15 to 20 CAPS patients. The study could include both pediatric and adult patients.

Variables and data sources

The primary endpoints of the study were:

- 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 were to 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 were:

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

The PRINTO network organized the data collection. The source for all data was the patients' medical records. The investigators verified the transfer of relevant prospective data to the eCRF designed for the study in a web-based data entry tool.

Results

The duration of the enrollment period was 1 year and 11 months. A total of 12 patients were included in this study. Of these, 1/12 patient initiated the Kineret treatment at baseline and 11/12 patients were already using the Kineret graduated prefilled syringe at baseline.

<u>Primary endpoint</u>

A total of 7 treatment emergent AEs were reported, of those 2/7 were considered treatment emergent serious adverse events (SAEs) due to the required hospitalization (1 tonsillitis and 1 urinary tract infection). All treatment emergent AEs were observed in 1 patient and considered unrelated to the Kineret treatment by the investigator.

No adverse events (AEs) were considered of severe intensity by the investigators, 6/7 AEs were considered of moderate severity and only 1 (14.3 %) was considered of mild severity.

All 7 reported AEs were infections: 5 tonsillitis, 1 urinary tract infection and 1 upper respiratory tract infection.

Secondary endpoint

The median (Q1; Q3) Kineret dose at Year 1, Year 2, Year 3 and Year >3 was 1.6 (1.5; 2.3), 1.6 (1.2; 2.0), 2.6 (1.7; 3.6) and 1.4 (1.1; 2.0) mg/kg/day, respectively.

In total, 6/12 patients permanently discontinued the Kineret treatment, of those 2 patients discontinued at Year 1, 3 patients at Year 2, and 1 patient at Year >3. There were no permanent discontinuations of Kineret at Year 3. The reasons for permanent discontinuation included change to another IL-1 blocking treatment (5/12 patients), inefficacy (1/12 patient) and non-compliance (1/12 patient). All 5 patients that transferred to another IL-1 blocking treatment reported to have switched to canakinumab.

Only 1 patient temporarily discontinued treatment with Kineret. The discontinuation occurred at Year 2, due to non-compliance. The patient discontinued treatment with Kineret after the laboratory results indicated that the patient had developed neutropenia. The neutropenia was assessed as a non-serious AE and the Kineret dose was adjusted. However, after registering the AE, the laboratory results were reviewed and the investigator confirmed that the patient did not have neutropenia as previously reported, and the Kineret treatment was reinstated to the original dose and the AE of neutropenia was deleted.

Discussion

This PASS was designed to address the effectiveness of the 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 also addressed 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).

An uncontrolled study design was deemed acceptable for this non-interventional PASS. Accordingly, the study design carried the general limitations inherent in an uncontrolled design regarding statistical analyses, interpretation, generalizability and conclusiveness, in addition to the threat of inherent bias. However, the primary endpoint was: rate of serious infections, rate of new malignancies, rate of ISRs, rate of allergic reactions and rate of medication errors including re-use of syringe; all of them are easy to measure objectively variables and do not require a subjective interpretation from the investigator, which minimizes the threat of bias although the study did not have a control group.

The AEs observed in this study are in line with the known safety profile for Kineret in CAPS patients. Based on the data observed in this study, the introduction of a pre-filled syringe with a graduated label for single-use injections do not seems to alter the risks for medication errors, including re-use of syringe, or others of the pre-specified risks.

Marketing Authorization Holder(s)

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