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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Orencia

abatacept

Procedure no: EMEA/H/C/000701/P46/064

Note

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

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1. Introduction

On 27 Februry 2019, the MAH submitted the final 24-month clinical study report for a paediatric polyarticular juvenile idiopathic arthritis (pJIA) study (study number IM101301) for ORENCIA, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

An interim report for study IM101301 was issued in January 2018; that interim report supported the application (procedure EMEA/H/C/000701/X/0117/G) for i) a new subcutaneous (SC) route of administration of abatacept for 2-17-year old patients (including thus also a totally new age group of 2-5-year olds into the SC-indication), as well as ii) positioning Orencia treatment in second line of pJIA treatment (i.e. removal of "following treatment failure with TNF-inhibitors" from the IV indication), and including also monotherapy in case of MTX intolerance or when treatment with MTX is inappropriate into the indication. A positive CHMP opinion was issued on 31 January 2019 for this procedure.

At the time of the interim report, 15 subjects in the 2 - 5 year age cohort were still ongoing in the 20-month long-term extension (LTE) period of the study, and provision of the current 24-month report was requested by CHMP as part of the assessment process of procedure EMEA/H/C/000701/X/0117/G. Provision of the complete 2-year data is also listed as an additional pharmacovigilance activity (Category 3) in the Risk Management Plan (RMP). In addition, provision of the report is considered by the MAH to fulfil the requirement of Art. 46 as it pertains to this study.

A clinical overview, summarising the results from the full 2-year data of the 2 - 5 and 6 - 17 year age cohorts, with a focus on the results from the 2 - 5 years age cohort, was also provided.

It should be noted that the study was extended for up to 5 years in some countries (Argentina, Germany, Italy, Belgium, France, and South Africa) by protocol amendment to ensure continued dosing for subjects who demonstrated clinical benefit from SC abatacept at the conclusion of the study; thus, the study is still partly ongoing.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study number IM101301, entitled "A phase 3 multi-center, open-label study to evaluate pharmacokinetics, efficacy, and safety of abatacept administered subcutaneously (SC) in children and adolescents with active polyarticular Juvenile Idiopathic Arthritis (pJIA) and inadequate response (IR) to biologic or non-biologic disease modifying anti-rheumatic drugs (DMARD)" is a stand-alone study.

The MAH stated that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, no further impact on the ORENCIA product information related to procedure EMEA/H/C/000701/X/0117/G (for which the Commission Decision was issued on 8 April 2019) was anticipated, as the 24-month results remain consistent with the data reviewed during the procedure.

2.2. Information on the pharmaceutical formulation used in the study

Abatacept (125 mg/mL sterile solution, ready for injection) was administered subcutaneously by prefilled syringe. The same syringe barrel (Hypak Physiolis 1 mL barrel) was used to manufacture the three prefilled syringe dosage strengths.

2.3. Clinical aspects

2.3.1. Introduction

As indicated above, an interim report for study IM101301 was issued in January 2018 to support an indication extension and new route of administration (SC) for paediatric use of ORENCIA for polyarticular juvenile idiopathic arthritis in patients 2 years and above (EMEA/H/C/000701/X/0117/G).

The interim report presented the complete results for the 2 - 5 year age cohort for the 4-month short-term (ST) period of the study, whereas a total of 15 subjects in the 2 - 5 year age cohort were still ongoing in the 20-month long-term extension (LTE) period at the time of database lock for the interim report (31-Mar-2017). Complete 2-year results for the 6 - 17 year age cohort for the 4-month ST period and the 24-month cumulative period (4-month ST period plus 20-month LTE period) were already presented in the interim report, with the exception of the following:

- Growth and Tanner stage analyses
- Complete biomarker analyses (thyroid-stimulating hormone [TSH], anti-glutamic acid decarboxylase [GAD], anti-thyroperoxidase [TPO]) including all 6-month post last treatment follow-up data for subjects who completed the 2-year LTE or discontinued in the 2-year LTE and who did not continue in the 5-year LTE.
- Complete immunogenicity and neutralising antibody analyses including all 6-month post last treatment follow up data for subjects who completed the 2-year LTE or discontinued in the 2-year LTE and who did not continue in the 5-year LTE.
- By-subject listing of adverse events (AEs) in the Study (all AEs from the extended long-term beyond year 2 that were not previously reported).

Within procedure EMEA/H/C/000701/X/0117/G, the CHMP made the following request: “At the time of submission of the final results (24-month and 5-year data) of the Study IM101301, the MAH should address the following safety aspects: MLA eosinophils, MLA (haematuria, RBC and WBC) in urine, the effect of MTX on ADA formation, age dependency of ADA response, AEs occurring within 24 hours in the pJIA studies, relatedness of AEs to study drug, immunogenic potential of the lubricant silicon oil.” Provision of the complete 2-year data was also listed as a Category 3 additional pharmacovigilance activity in the RMP.

The focus of the current assessment was to evaluate safety aspects as identified by the CHMP, as well as to assess newly reported data for consistency as compared to the interim report. An exhaustive re-review of data previously assessed within the completed procedure EMEA/H/C/000701/X/0117/G has not been included.

2.3.2. Clinical study

Study IM101301

Description

Study IM101301 was a Phase 3 multi-centre, open-label study to evaluate pharmacokinetics, efficacy, and safety of SC abatacept in children and adolescents with active pJIA and an inadequate response to biologic or non-biologic DMARDs. The study comprised a 4-month ST period followed by a 20-month LTE.

The study was extended for up to 5 years in Argentina, Germany, Italy, Belgium, France, and South Africa by protocol amendment to ensure continued dosing for subjects who demonstrated clinical

benefit from SC abatacept at the conclusion of the study; however, no efficacy or PK data is being collected beyond the 20-month LTE.

According to the MAH, the study focused primarily on paediatric subjects aged 6 - 17 years with active pJIA who had an inadequate response to at least 1 biologic or non-biologic DMARD. The purpose of the study was to evaluate if 4 months of a weekly weight-tiered SC abatacept dosing regimen would deliver steady-state systemic exposures within the therapeutic range associated with maximal efficacy observed with intravenous (IV) abatacept in paediatric subjects aged 6 - 17 years with active pJIA who were resistant to at least one biologic or non-biologic DMARD. The study included 2 cohorts of subjects with active pJIA: a 2 - 5 year age cohort and a 6 - 17 year age cohort.

Methods

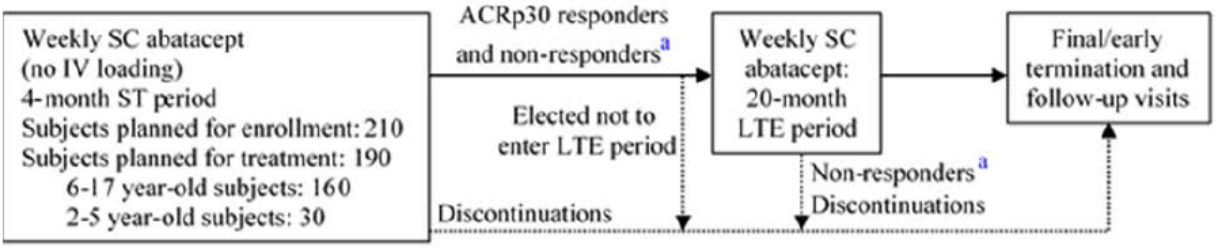
Objective(s)

The overarching objective of the study was to assess pharmacokinetics, efficacy and safety in children and adolescents ages 2 - 17 years with pJIA following 4 months of ST and 20 months of LT open label abatacept SC therapy.

Study design

The study was a non-comparative, open label study, comprising a 4-month ST period, followed by a 20-month LTE. See **Figure 1** for a graphical depiction.

Figure 1. IM101301 - Study Design



[a] Non-responders per American College of Rheumatology pediatric (ACRp) 30 criteria by month 4 were given the opportunity to be treated with SC abatacept for an additional 3 months in the LTE period. If, after 7 total months of treatment, response did not occur, the subject was considered for discontinuation.

Subjects were permitted to remain on background treatment with stable doses of MTX (permitted dose range was 10-30/mg/m2/week with an absolute maximum dose of 40 mg/week), corticosteroids and NSAIDs, but other conventional synthetic DMARDs as well as biological DMARDs were to be terminated with specific wash-out periods before initiation of study medication.

Subjects were treated with open-label abatacept for a 4-month ST period and evaluated for safety and immunogenicity. Subjects who completed the ST period were given the option to enter a 20-month LTE period during which they continued to receive weekly SC abatacept injections. Subjects who entered the LTE period as non-responders per ACR Pediatric 30 criteria were given the opportunity to be treated with SC abatacept for an additional 3 months. Treatment was discontinued if an individual subject did not achieve ACR Pediatric 30 status after a total of 7 months of abatacept therapy (4-month ST period plus 3 months of LTE period).

The study protocol was amended in some countries to extend the study for up to 5 years to ensure continued dosing for subjects who demonstrated clinical benefit from SC abatacept at the conclusion of the study. However, no efficacy or PK data is being collected beyond the 20-month LTE.

Study population /Sample size

Key inclusion criteria for the study were:

- ages 2 to 17 years, male or female
- diagnosed with active pJIA, extended oligoarthritis, enthesitis-related arthritis, systemic arthritis (with a polyarticular course), or psoriatic arthritis (PsA), but with no other rheumatic disease
- an insufficient therapeutic response (for ≥ 3 months) or prior intolerance to at least 1 biologic or non-biologic DMARD
- a history of at least 5 joints with active disease
- active articular disease with ≥ 2 active joints and ≥ 2 joints with limitation of movement at baseline

Subjects with prior inadequate response to at least one TNFα antagonist or other biologic DMARD were restricted to no more than 30% of the study population. Subjects with systemic pJIA at onset were restricted to no more than 10% of the study population.

Key exclusion criteria included:

- previous treatment with CTLA4Ig or abatacept
- failure on more than two TNFα antagonists or other biologic DMARDs
- presence of an active infection, serious infections or history of frequent infection or chronic infections within 3 months prior to the first dose of study medication
- severe concomitant medical comorbodity

The planned sample size was 160 subjects in the 6 - 17 year age cohort and 30 subjects in the 2 - 5 year age cohort.

- A sample size of 160 subjects aged 6 - 17 years was planned for the primary analysis to allow assessment of the PK parameters as well as the safety and efficacy of SC abatacept in pJIA; it approximated the sample size of the 4-month open-label lead-in phase of the original IV pJIA abatacept study, allowing an evaluation of the PK, safety, efficacy, and immunogenicity of SC abatacept in pJIA with similar precision as previously obtained for IV abatacept (Period A of Study IM101033).
- A sample size of 30 subjects aged 2 - 5 years was predicted to permit descriptive assessments of PK, efficacy, and safety response.

Treatments

Open-label SC abatacept was administered by prefilled syringe (PFS) once weekly as a weight-tiered dose regimen:

- 10 to < 25 kg: 50 mg in 0.4 mL PFS
- 25 to < 50 kg: 87.5 mg in 0.7 mL PFS
- ≥ 50 kg: 125 mg in 1.0 mL PFS

Outcomes/endpoints

The primary endpoint of the study was abatacept Cminss at Day 113 in 6 - 17 year old subjects.

The secondary endpoints were:

- Proportion of subjects achieving ACR Pediatric 30 at Day 113 in 6 - 17 year old subjects. ACR Pediatric 30 response was defined as:
    - ≥ 30% improvement in at least 3 of the 6 pJIA core set variables (number of active joints, number of joints with limitation of motion, physician global assessment of disease activity, parent global assessment of patient overall well-being, functional ability as measured by the Children's Health Assessment Questionnaire (CHAQ), and CRP)

    and

    - ≥ 30% worsening in not more than 1 of the remaining 6 pJIA core set variables
- Abatacept Cmin at Day 57 Day 85, and Day 113 during the initial 4-month short term period by each weight-tiered dosing regimen in 6 - 17 year old subjects.
- Safety summary (proportion of subjects with adverse events, deaths, SAEs, and AEs leading to discontinuation) during initial 4-month ST (6 - 17 year age cohort only) and during cumulative abatacept period (ST and LTE periods combined) in both age cohorts.
- Proportion of subjects with positive immunogenicity response during initial 4 month (6 - 17 age cohort only) and during the cumulative abatacept period up to 6 months following discontinuation of treatment (in both age cohorts).

Exploratory endpoints (for both age [2 - 5 and 6 - 17] cohorts, unless indicated otherwise) included:

- Abatacept Cmin over time
- Changes from baseline in individual components of ACR Pediatric 30 over time
- Proportion of subjects achieving ACR Pediatric 30, 50, 70, 90, 100 and inactive disease rates over time
- Proportion of subjects achieving ACR Pediatric 30 response rates at Day 113 by weight and by TNF naive and TNF-inadequate response (IR) subgroups, by JIA subtypes and for whole population after exclusion of systemic JIA patients in the 6 - 17 year old subjects
- Assessment of anti-GAD and anti-TPO autoantibodies and TSH during treatment and up to 6 months following discontinuation of treatment
- Characterisation of PK of SC abatacept in pJIA using population PK analysis and exposure-response relationship
- Assessment of change in growth and Tanner stage
- Assessment of improvement in the parent version of the Activity Limitation Questionnaire over time

Statistical Methods

All efficacy analyses were descriptive, and no formal statistical testing took place. The various response rates were summarised with a point estimate and a 95% confidence interval (CI). The evaluation of drug safety was based on clinical AEs and laboratory abnormalities reported during the

study. Growth analysis was based on changes from baseline to Year 2 in in WHO-standardised z-score for height and body mass index (BMI).

CHMP comments:

Study IM101301 was a part of the agreed Paediatric Investigation Plan for ORENCIA. The underlying approach, in which limited data was to be collected in the target population within study IM101301, and with parallel extrapolation of efficacy and safety data from source populations of other abatacept development programmes (abatacept IV and SC in RA, and abatacept IV in pJIA), was agreed on with the Paediatric Committee.

Within procedure EMEA/H/C/000701/X/0117/G, the CHMP considered the design of the study acceptable.

Results

Recruitment / Number analysed

In total, 173 subjects in the 6 - 17 year age cohort received at least 1 dose of study drug, and efficacy and safety were assessed for the all treated subjects population (173 subjects). Forty-six (46) subjects were treated in the 2 - 5 year age cohort, and all 46 subjects were evaluated for efficacy and safety.

Baseline data

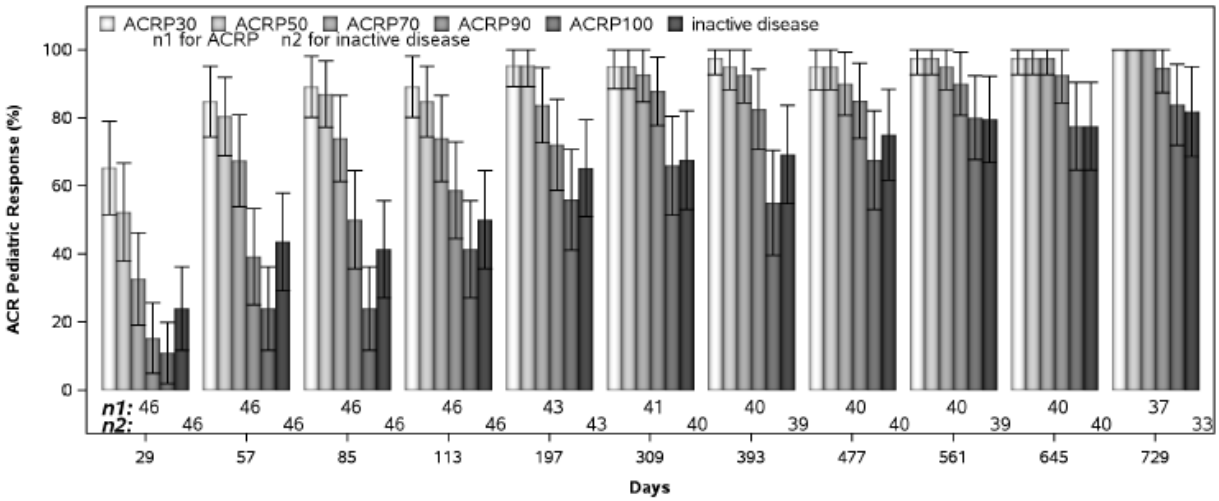
In both age cohorts, the majority of treated subjects were white females. In the 2 - 5 year age cohort, median age was 4.0 years (range 2 - 5 years) and 43/46 (93.5%) of treated subjects weighed < 25 kg. In the 6 - 17 year age cohort, median age was 13.0 years (range 6 - 17 years) and 155/173 (89.6%) of treated subjects weighed ≥ 25 kg.

Efficacy results

LTE efficacy in 2 -5 year old subjects

Compared to previously reported interim results in the 2 - 5 year age cohort, there were no substantial differences for the different ACR Paediatric responder categories. Thus at Day 729, the proportions of ACR Paediatric 90, ACR Paediatric 100, and inactive disease responders in the as-observed analysis were 94.6%, 83.8%, and 81.8%, respectively (**Figure 2**); this compares favourably to rates of 90.9% for ACR Paediatric 90, and 77.3% for ACR Paediatric 100 and inactive disease reported in the interim report.

Figure 2. Proportion of ACR Paediatric Responses Over Time During the Cumulative Period - All Treated Subjects - 2 - 5 Year Age Cohort



Inactive disease status is defined as no active joints, physician's global assessment of disease severity <=10 mm and CRP <=0.6mg/dl.
Up to Day 113, a non-responder imputation is applied, except if missing measurement between 2 timepoints for which a response is observed.
In that case a responder is imputed. After Day 113, as observed.

Results on the JRA/JIA core set variables of Active joints, Joints with loss of motion, and Physician's global assessment of disease severity remained essentially unchanged from the interim report, with mean % improvements at Day 729 exceeding 95% for these variables.

Scores on the parental assessment of overall well-being and Children's Health Assessment Questionnaire (CHAQ) were improved compared to the interim report: in the interim analysis, 24.3% and 36.4% mean improvements, respectively, were reported from baseline to Day 729. In the current final 24-month report, the corresponding mean % improvements from baseline to Day 729 were 47.5% and 53.0%, respectively.

CHMP comments:

Compared to the interim data assessed within procedure EMEA/H/C/000701/X/0117/G, there was no signal of unexpected loss of efficacy within the 2 -5 year age cohort. Scores on the parental assessment of well-being and on the CHAQ were improved compared to those presented in the interim analysis.

Safety results

Subject disposition

In the 2 - 5 year age cohort, 39 (84.8%) subjects completed the cumulative period and 7 (15.2%) subjects discontinued (Table 1).

In the 6 - 17 year age cohort, 132 (76.3%) subjects completed the cumulative period, 36 (20.8%) subjects discontinued, and 5 (2.9%) subjects completed the ST period without entering the LT period.

In both age cohorts, the most common reason for discontinuation was lack of efficacy (5 subjects [10.9%] in the 2 - 5 year age cohort and 17 subjects [9.8%] in the 6 - 17 year age cohort).

Table 1. Subject Disposition - 2 - 5 Year Age Cohort

	Number %) of Subjects N = 46
No. of Subject Discontinued	7 (15.2)
Death	0
Adverse Event	1 (2.2)
Lack of Efficacy	5 (10.9)
Administration reason by sponsor	1 (2.2)
No. of Subjects Enrolled	47
No. of Subjects Treated	46
No. of Subjects Completed Cumulative Period	39 (84.8)

Extent of exposure

For the 46 subjects who entered into the study in the 2 -5 year age cohort, the mean (SD) exposure to SC abatacept over the cumulative period was 22.3 (6.2) months with a median duration of 24.3 months (**Table 2**). The subjects received a median of 102 SC injections during the cumulative period; 16 subjects (34.8%) received all scheduled injections during the cumulative period, whereas 11 subjects (23.9%) missed more than 3 injections.

Table 2. Extent of Exposure (Number of Months) to Subcutaneous Abatacept During the Cumulative Period: All Treated Subjects – 2 - 5 Year Age Cohort

	Number (%) of Subjects
Months of Exposure	Total (N=46)
<2	0
2 - <4	0
4 - <6	3 (6.5)
6 - <9	1 (2.2)
9 - <12	1 (2.2)
12 - <15	1 (2.2)
15 - <18	0
18 - <21	0
21 - <24	2 (4.3)
>=24	38 (82.6)
Mean Months of Exposure (SD)	22.3 (6.21)
Median (Range)	24.3 (4.0 - 26.2)

Interruptions in therapy were not deducted from calculation of months of exposure.
For subjects who discontinued the cumulative period, completed the cumulative period and not entered the LT extension beyond year 2, or completed the short-term without entering the LT: Months of Exposure = [(date of last dose in the Cumulative Period - date of first dose in the study + 1) - adjustment + 56]/30.
For subjects who continue in the Long-term period extension beyond year 2, Days of Exposure = (date of first dose in the Long-term
Extension Period - date of first dose in the study).
For subjects who continue beyond the cutoff date, Months of Exposure = [(cutoff date - date of first dose in the study + 1)- adjustment]/30.
Adjustment is the time span in excess of 56 days: between the last dose in short-term and the first dose in the long-term period.

CHMP comments:

Within the 2 - 5 year age cohort, the percentage of subjects completing the cumulative period (84.8%) was higher than the 76.3% reported for the 6 - 17 year age cohort. The mean extents of exposures were comparable between the age cohorts (21.8 (SD 6.9) months for the 6 - 17 year age cohort, and 22.3 (SD 6.2) months for the 2 - 5 year age cohort).

Concomitant anti-rheumatic therapies - 2 - 5 year age cohort

The use of concomitant anti-rheumatic medications is summarised in **Table 3**. Over 80% of subjects were receiving concomitant MTX during participation in the study. A total of 3 subjects began use of excluded biologic DMARDs after Day 1; all 3 subjects began use of excluded biologic DMARD after discontinuation from the study drug but within the 56-day post-treatment observation period.

Table 3. Anti-Rheumatic Medications Summary During the Cumulative Period up to 56 Days Post the Last Dose in the Cumulative Period - All Treated Subjects – 2 - 5 Year Age Cohort

	Number (%) of Subjects
	Total (N=46)
Total Subjects on CONMEDs	45 (97.8)
NSAIDS	37 (80.4)
DMARDS	38 (82.6)
Methotrexate	38 (82.6)
Biologics	3 (6.5)
Tocilizumab	2 (4.3)
Etaneroept	1 (2.2)
Corticosteroids	
Oral and/or injectable	15 (32.6)
Oral	14 (30.4)
Mean Oral Dose (SD)	5.7 (4.22)

The mean oral dose of corticosteroids (prednisone equivalents) includes only subjects who have taken at least 1 dose of oral corticosteroids.
Includes data from the day of the first subcutaneous injection in the short-term period up to the day of the last subcutaneous injection in the cumulative period + 56 days or the first day of long-term extension period, whatever comes first.

New safety observations - 2 - 5 year age cohort

Compared to data presented in the interim analysis, the overall safety profile remained essentially unchanged. A summary of subjects with AEs is provided in **Table 4**; compared to the previously reported data, 2 additional SAEs (1 drug-related) were reported. The newly reported SAEs were:

1) a limb abscess in one subject; this SAE occurred on Day 674 and was assessed as severe in intensity and related to study drug. The abscess was surgically excised and the event resolved on Day 685. Study drug was interrupted from Day 666 until Day 685.

2) cellulitis in one subject; this SAE occurred on Day 664, was assessed as moderate in intensity and unrelated to study drug. The event was reported as having resolved, with a duration of 12 days.

Table 4. Summary of Subjects with Adverse Events Reported During the Cumulative Period - All Treated Subjects – 2 - 5 Year Age Cohort

Category	Number (%) of subjects (n=46)
Deaths	0 (0.0)
SAEs	5 (10.9)
SAEs Related to Study Drug	2 (4.3)
Discontinuations Due to AEs	1 (2.2)
Discontinuations Due to SAEs	0 (0.0)
AEs of Special Interest	
Malignancies	0 (0.0)
Autoimmune Events	0 (0.0)
Local Injection-site Reactions	2 (4.3)
AEs Within 24 Hours of Drug Administration	26 (56.5)
Infections	40 (87.0)
Overall AEs	44 (95.7)
AEs Related to Study Drug	30 (65.2)

Compared to the interim report, there were no new AEs leading to study drug discontinuation and no new injection site reactions. No malignancies or autoimmune disorders were reported for the 2 - 5 year age cohort during the cumulative period, including no cases of uveitis.

There were 4 additional infections reported, bringing the total to 40 subjects. The percentage of infections was higher in the 2 - 5 year age cohort (87.0%) than the 6 - 17 year age cohort (68.2%). The most commonly reported infections in the 2 - 5 year age cohort were nasopharyngitis (17 subjects, 37.0%), upper respiratory tract infection (10 subjects, 21.7%), rhinitis (8 subjects, 17.4%), pharyngitis (6 subjects, 13.0%), and gastroenteritis (6 subjects, 13.0%). Most subjects reported single occurrences of an infection or infestation. Six subjects (13.0%) reported 2 to 3 occurrences of nasopharyngitis, and 4 subjects (8.7%) reported at least 4 occurrences of nasopharyngitis.

According to the MAH, a review of the AEs against the recently standardised list of "indicator infections" (opportunistic infections and infections possibly indicative of immunosuppression) did not identify opportunistic infections in this cohort.

Overall, AEs were reported in 95.7% (44/46) of 2 - 5 year old subjects during the cumulative period, compared to 93.5% (43/46) in the interim report. The most frequently reported (≥ 10% of subjects) AEs were in the SOC Infections and infestations. All reported AEs were mild or moderate in severity, except the severe SAE of limb abscess (summarised above). AEs with an incidence of > 10 subjects per 100 person-years were nasopharyngitis, pyrexia, upper respiratory tract infections, cough, and rhinitis. **Table 5** summarises the most frequently reported unique adverse events.

Table 5. Frequently Reported (≥ 10% of Subjects) Adverse Events During the Cumulative Period – 2 - 5 Year Age Cohort

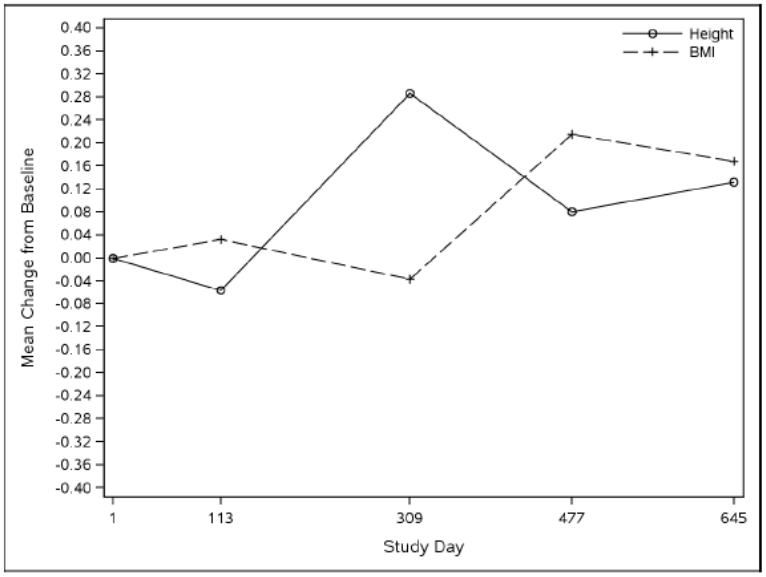
System Organ Class Preferred Term	Number (%) of subjects (n=46)
Nasopharyngitis	17 (37.0)
Pyrexia	15 (32.6)
Upper Respiratory Tract Infection	10 (21.7)
Cough	9 (19.6)
Rhinitis	8 (17.4)
Conjunctivitis	6 (13.0)
Gastroenteritis	6 (13.0)
Headache	6 (13.0)
Nausea	6 (13.0)
Pharyngitis	6 (13.0)
Vomiting	6 (13.0)

The most frequently observed major laboratory abnormalities (MLA) in the 2 - 5 year age cohort were white blood cells (WBC) in the urine (35.7%), high eosinophils (30.4%) and low serum glucose (21.7%), followed by elevated creatinine (15.2%), elevated leukocytes (10.9%) and elevated potassium (8.7%). According to the MAH, abnormal laboratory values typically reverted to within normal ranges during continued treatment, and few subjects had persistent MLA for 2 or more consecutive laboratory test days.

All subjects in the 2 - 5 year age cohort had negative anti-GAD and anti-TPO and normal TSH at baseline. During the cumulative period post-baseline, 1 positive anti-GAD value was observed on Day 113 and 1 was observed on Day 477 post-first dose; both subjects returned to negative status at the next visit. None of the subjects had a positive post-baseline anti-GAD value on Day 85 and Day 169 post-last-dose. Positive anti-GAD was not associated with any autoimmune thyroid-related events or autoimmune type I diabetes. None of the subjects had a positive anti-TPO value or an abnormal TSH value post-baseline in the 2 - 5 year age cohort.

In the 2 -5 year age cohort, standardised height and standardised BMI slightly increased from baseline during the cumulative 2-year treatment (**Figure 3**).

Figure 3. Standardised Height and BMI- Mean Change from Baseline During Cumulative Period: All Treated Subjects - 2 - 5 Year Age Cohort



HT (n)	46	41	41	40	39
BMI (n)	46	41	41	40	39

In the 2 - 5 year age cohort, 10.9% (5/46) and 37.5% (3/8) of the subjects tested positive for antibodies to abatacept relative to baseline on-treatment and post-last dose, respectively, during the cumulative period (**Table 6**). Titres for all but 1 subject were ≤ 155; the highest titre observed for this subject was 1940 at 85 days post last treatment. There was no increase in immunogenicity incidence over time.

Table 6. Proportion of Subjects with Positive Immunogenicity Response Relative to Baseline (ECL Method) During Cumulative Period - Immunogenicity Population - 2 - 5 Year Age Cohort

Study Day	CTLA4 AND POSSIBLY IG n/m (%)	IG AND/OR JUNCTION REGION n/m (%)	Total n/m (%)
Day 57	0 / 44	2 / 44 (4.5%)	2 / 44 (4.5%)
Day 85	0 / 43	1 / 43 (2.3%)	1 / 43 (2.3%)
Day 113	0 / 40	1 / 40 (2.5%)	1 / 40 (2.5%)
Day 309	1 / 41 (2.4%)	1 / 41 (2.4%)	2 / 41 (4.9%)
Day 477	0 / 36	0 / 36	0 / 36
Day 645	1 / 37 (2.7%)	0 / 37	1 / 37 (2.7%)
Day 729	1 / 32 (3.1%)	0 / 32	1 / 32 (3.1%)
Overall on Trt	2 / 46 (4.3%)	3 / 46 (6.5%)	5 / 46 (10.9%)
28 days post last dose	0 / 6	0 / 6	0 / 6
85 days post last dose	1 / 6 (16.7%)	1 / 6 (16.7%)	2 / 6 (33.3%)
168 days post last dose	1 / 6 (16.7%)	0 / 6	1 / 6 (16.7%)
Overall Post Visits	2 / 8 (25.0%)	1 / 8 (12.5%)	3 / 8 (37.5%)
Overall	4 / 46 (8.7%)	3 / 46 (6.5%)	7 / 46 (15.2%)

Of the 5 subjects testing positive while on-treatment, 2 had no missed doses within 1 year prior to positive sample, one subject had 1 missed dose and 2 subjects had 2 consecutive missed doses within 1 year prior to positive sample. During the cumulative on-treatment period, 2 subjects had a persistent immunogenicity response (defined as 2 or more consecutive positive test results relative to baseline with the same antibody reactivity). There was no apparent association between positive antibody response and loss of efficacy or worsening safety results. In one subject, a Cmin value of < 10 µg/mL was reported at days 645 and 729. A positive immunogenicity response was detected at the same time points for this subject, but the subject remained an ACR Pediatric 100 responder and in inactive disease status at both time points.

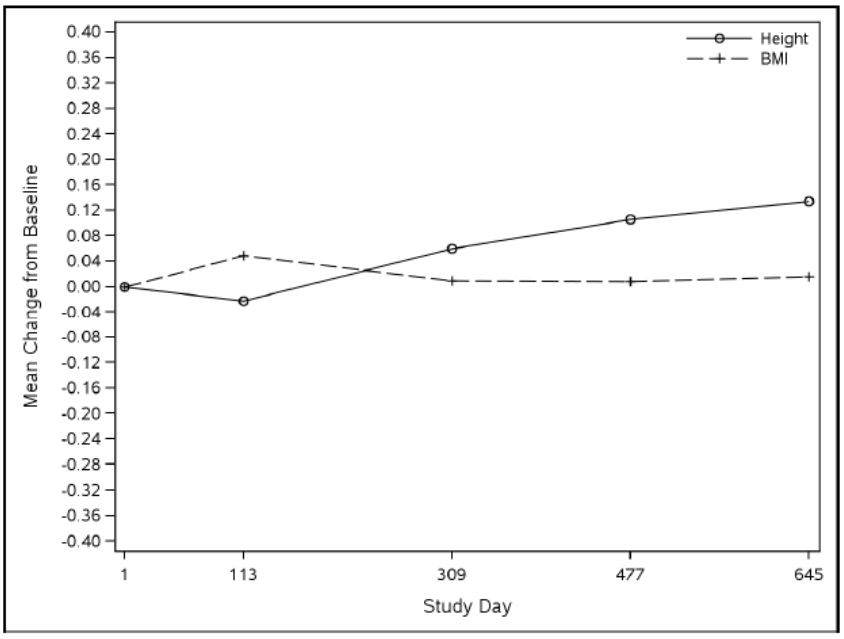
New safety observations - 6 - 17 year age cohort

According to the MAH, the summary of AEs included in the interim report was already complete for the 2-year data up to Day 56 post-last treatment for the 6 - 17 year age cohort. A listing of AEs reported since the interim report, mostly comprising newly reported AEs beyond year 2, was created for the 24 month report. According to the MAH, there were no new safety signals. All new or updated AEs since the interim report were mild or moderate in intensity, and in the MAH's review of the AEs beyond year 2, there were no clinically relevant findings.

There were no changes in the anti-TPO, anti-GAD and TSH results compared to the interim report. In total, 6 positive anti-GAD or anti-TPO antibody values were observed in 4 subjects with negative values at baseline; these were not associated with any autoimmune thyroid-related events or type I diabetes. One subject (0.7%) had a shift from normal TSH at baseline to elevated TSH on Day 477. None of the subjects had a shift from normal at baseline to elevated TSH 85 days or 169 days post last dose.

In the 6 - 17 year age cohort, standardised height increased and standardised BMI was maintained during the cumulative 2-year treatment (**Figure 4**). No inhibition was seen on Tanner developmental staging in this age cohort after 2 years cumulative treatment.

Figure 4. Standardised Height and BMI- Mean Change from Baseline During Cumulative Period: All Treated Subjects - 6 - 17 Year Age Cohort



HT (n)	173	161	147	140	125
BMI (n)	173	161	147	140	125

There were no changes in the immunogenicity data in the 6 - 17 year age cohort compared to the interim report. Overall, 8/172 subjects (4.7%) developed a positive response relative to baseline; of these, 4/172 subjects (2.3%) had a positive response while on treatment, and 6/42 subjects (13.6%) had a positive response post treatment.

Specific safety aspects as identified by CHMP

1. MLA eosinophils

Consistent with findings in the interim report, a high eosinophil count remained a frequent observation, with an elevated count observed in 14/46 subjects (30.4%) in the 2 -5 year age cohort

(vs. 12/26 (26.1%) in the interim report). Similar to the previous observation, the elevated counts were typically self-limiting and transient and were not associated with clinical AEs.

According to the MAH, there was no definitive cause for many of the reported MLAs for eosinophils, but a high incidence of upper respiratory infections was noted in both age cohorts during the cumulative period of the study, especially in the 2 - 5 year age cohort, and viruses such as rhinovirus and respiratory syncytial virus that are very common in young patients can be associated with eosinophilia. No subject with an MLA of eosinophilia had an anaphylactic reaction or an AE related to allergies in either age cohort. According to the MAH, seasonal allergies may have played a contributing role for the MLA values of eosinophilia in this global trial; 12 (26.1%) of 46 subjects 2 - 5 years of age used concomitant respiratory medications (including antihistamines, anti-asthmatic, and nasal, cough and cold, and throat preparations) during the cumulative period.

2. MLA (haematuria, RBC and WBC) in urine

In the 2 - 5 year age cohort, urine WBC were observed in 10/28 (35.7%) of subjects, compared to 8/25 (32.0%) of subjects as reported in the interim analysis. Urine RBCs were infrequent in this age cohort and observed in 1/25 (4.0%) of subjects, compared to 0/22 of subjects in the interim analysis. No new data was provided for assessment for the 6 - 17 year age cohort.

According to the MAH, possible reasons for the urinary abnormalities of RBCs, WBCs, and blood that met the MLA criteria include AEs associated and not associated with the genitourinary tract, events from past medical history, and/or menstruation in young girls.

3. Effect of MTX on ADA formation

Of the 36 subjects in the 2 - 5 year age cohort who were on MTX, 7 (19.4%) tested positive for antibodies to abatacept relative to baseline in the cumulative period; none of the 10 subjects who did not receive MTX tested positive for antibodies to abatacept relative to baseline in the cumulative period (**Table 7**). Three out of 4 subjects with antibodies specific to CTLA4 and possibly Ig had samples tested for neutralising antibodies; 2 were positive for neutralising antibodies during post treatment visits.

Table 7. Summary of Immunogenicity According to MTX Treatment for Subjects in the 2 - 5 Year Age Cohort

MTX at Day 1	Period	CTLA4 and Possibly Ig (rate)	Ig and/or Junction Region (rate)	Total (rate)
Yes	On Treatment	2/36 (5.6%)	3/36 (8.3%)	5/36 (13.9%)
	Post Visits	2/6 (33.3%)	1/6 (16.7%)	3/6 (50.0%)
	Overall	4/36 (11.1%)	3/36 (8.3%)	7/36 (19.4%)
No	On Treatment	0/10	0/10	0/10
	Post Visits	0/2	0/2	0/2
	Overall	0/10	0/10	0/10

Of the 135 subjects in the 6 - 17 year age cohort who were on MTX, 8 (5.9%) tested positive for antibodies to abatacept relative to baseline in the cumulative period; none of the 37 subjects who did not receive MTX tested positive (**Table 8**). Three out of 5 subjects with antibodies specific to CTLA4 and possibly Ig had samples tested for neutralising antibodies; none were positive for neutralising antibodies.

Table 8. Summary of Immunogenicity According to MTX Treatment for Subjects in the 6 - 17 Year Age Cohort

On MTX at Day1	Period	CTLA4 and Possibly Ig (rate)	Ig and/or Junction Region (rate)	Total (rate)
Yes	On Treatment	1/135 (0.7%)	3/135 (2.2%)	4/135 (3.0%)
	Post-Visit	4/37 (10.8%)	2/37 (5.4%)	6/37 (16.2%)
	Overall	5/135 (3.7%)	3/135 (2.2%)	8/135 (5.9%)
No	On Treatment	0/37	0/37	0/37
	Post-Visit	0/7	0/7	0/7
	Overall	0/37	0/37	0/37

Abbreviations: CTLA4, cytotoxic T Lymphocyte-Associated Antigen 4; Ig, immunogeicity; MTX, methotrexate

According to the MAH, the number of subjects on MTX treatment at Day 1 was 3.6 times that of those not on MTX at Day 1 for both age cohorts; therefore, although immunogenicity incidence was higher for groups on MTX treatment on Day 1, it cannot conclusively be determined if MTX treatment on Day 1 had an impact on immunogenicity. According to the MAH, the overall incidence was low irrespective of age cohort or if subjects had received MTX-treatment at Day 1, and there was no measurable clinical impact.

4. Age dependency of ADA response

Overall, 15 out of 218 (6.9%) subjects had a positive immunogenicity response relative to baseline during the cumulative period of the study. Across the cumulative period, in the 6 - 17 year age cohort, 8 (4.7%) of 172 tested subjects developed anti-abatacept antibodies; 5 (2.9%) subjects were positive for CTLA4 and possibly Ig, and 3 (1.7%) subjects developed antibodies specific to the Ig and/or junction region of abatacept. The titres for all positive results were ≤ 176 and generally transient (i.e., not positive on ≥ 2 consecutive test dates), and no neutralising antibodies were detected. In the 2 - 5 year age cohort, 7 (15.2%) of 46 tested subjects developed anti-abatacept antibodies; 4 (8.7%) subjects had antibodies specific to CTLA4 and possibly Ig, of which 1 had 2 consecutive positive results tested for neutralising antibodies (1 tested negative for neutralising antibodies and 1 sample was not tested), 2 subjects each had 1 positive sample with neutralisation activity and 1 subject was not tested. Three (6.5%) subjects developed antibodies specific to the Ig and/or junction region; titres for all but 1 subject were ≤ 155.

According to the MAH, efficacy, safety, and PK were similar between subjects with and without positive immunogenicity response to abatacept, no AEs were attributed to an immune-mediated event in subjects with positive immunogenicity and the results indicate no clinical relevance for the detected ADAs. Although these numbers indicate a higher incidence in the 2 - 5 year age cohort, the difference in sample size makes it difficult to determine if the differences are meaningful, especially since in both cohorts ADA had no measurable clinical impact.

5. AEs occurring within 24 hours in the pJIA studies

Compared to the interim report, no new AEs occurring within 24 hours of study drug administration were reported in the study.

6. Relatedness of AEs to study drug

In the cumulative period, 30/46 (65.2%) subjects in the 2 - 5 year age cohort and 54/173 (31.2%) subjects in the 6 - 17 year age cohort had AEs assessed to be related to study drug. According to the MAH, the imbalance in AEs related to study drug between the two age cohorts is mostly due to the difference in within the SOC Infections and Infestations. Subjects in the 2 - 5 year age cohort had a

higher percentage of infections (52.2%) compared to subjects in the 6 - 17 year age cohort (20.8%). The percentage of infections was higher in the younger age cohort because upper respiratory tract infections (ear, nose, and throat) are the most common pathology in children 6 months to 6 years of age. Children less than 6 years of age also have a high prevalence of infections due to recurrent respiratory infections from their exposure to other children, attendance at day care and exposure to new pathogens. The MAH concluded that, with the exception of expected age-related differences (i.e., increased infections in the younger age cohort), the safety profiles were similar in both age cohorts.

7. Immunogenic potential of the lubricant silicon oil

No specific follow-up was provided on the possible immunogenic effect/adjuvant potential of the silicon oil contained in the different types of syringes.

Pharmacokinetic results

As seen in **Table 9**, the abatacept trough concentrations in the 2 - 5 year age cohort remained stable over time, and there was very little change compared to data in the interim report. Beyond Day 113, individual Cmin levels below the target therapeutic exposure level of 10 ug/mL were noted in 2 evaluable subjects. As noted above, a Cmin value of < 10 µg/mL was reported for one subject on days 645 and 729 concurrently with detection of a positive immunogenicity response; this subject had missed 2 consecutive weekly doses 35 and 42 days prior to Day 645.

Table 9. Summary Statistics of Abatacept Cmin Values during the Cumulative Period: Evaluable PK Population - 2 - 5 Year Age Cohort

	CMIN (ug/mL)						
STATISTIC	DAY 57	DAY 85	DAY 113	DAY 309	DAY 477	DAY 645	DAY 729
N	40	37	31	32	32	31	28
MEAN	49.7	52.1	52.9	45.9	52.9	57.4	55.1
S.D.	17.3	18.7	20.5	19.6	24.2	25.8	20.7
GEO. MEAN	47.1	49.1	49.6	42.1	47.5	51.4	45.5
%CV	35	36	39	43	46	45	38
MEDIAN	47.3	51.0	51.4	40.2	51.3	55.3	52.2
MIN	21.4	19.6	20.1	16.9	9.5	9.2	0.3
MAX	114.4	118.8	122.1	100.8	128.0	131.7	103.7

2.3.3. Discussion on clinical aspects

The 24-month study report provided updated complete data for the LTE period in the 2 - 5 year age cohort and summarised previously unreported data for the 6 - 17 year age cohort. Overall, the newly reported data are consistent with the interim report assessed as part of completed procedure EMEA/H/C/000701/X/0117/G, and evidence of treatment benefit of SC abatacept in the younger age cohort remains robust within the updated data. It is noted that in both age cohorts, the most common reason for discontinuation was lack of efficacy (5 subjects [10.9%] in the 2 - 5-year age cohort and 17 subjects [9.8%] in the 6 - 17 year age cohort). On request, the MAH discussed the lack of efficacy, resulting in discontinuation, seen in the current SC study (IM101301) and compared it to previous paediatric studies, particularly study IM101033 using intravenous abatacept, to determine whether the mode of administration of abatacept (SC versus IV) could have a possible role in the lack of efficacy observed. It was concluded that the currently available data, namely, the available comparative data, is scarce and fragmented, therefore, firm conclusion cannot be drawn. Thus, this issue should be revisited when the 5-year follow-up data becomes available. The MAH is expected and has agreed to provide these data as a separate post-authorisation commitment by the date specified in the RMP.

With regard to safety, the signals already noted during review of the interim data remain largely unchanged, and the frequency of drug-related AEs as well as the frequency of ADAs remain higher in

the 2 - 5 year age cohort compared to the 6 - 17 year age cohort. The difference in drug-related AEs still seems to be largely accounted for by the difference in infectious AEs, and the MAH's previously accepted explanation of this difference being due to an increased general frequency of upper respiratory tract infections in this age cohort still seems acceptable. In particular, there is no additional evidence of any iatrogenic effect in the 24-month report. However, it is recognised that two previously reported infectious SAEs in the paediatric population (varicella and sepsis) are individually identified in Section 4.8 of the current SmPC; as the experience from the 2 - 5 year age cohort still remains very limited, the MAH justified acceptably that the single SAE, limb abscesses, should be individually described in the SmPC Section 4.8. However, the overall available data on the single SAE of cellulitis does not justify inclusion the SmPC.

Moreover, the study demonstrated a very high general level of infections throughout the paediatric population, with younger children (2-5 years) being more affected than the older cohort. In line with these data, the MAH agreed to add a text to the SmPC stating that a higher incidence of infection (87.0% vs 68.2%), mostly upper respiratory tract infections, was reported in younger children with pJIA (2 to 5-year old) treated with SC abatacept compared to older children with pJIA (6 to 17-year old).

There is no new aggravating information regarding the immunogenicity of abatacept in the 2 - 5 year age cohort compared to the interim data. The ADA frequency remains indeed higher in the 2 - 5 year age cohort on-treatment (10.9% versus 2.3% in the older group), and especially in the post-treatment phase (37.5% versus 13.6%). Acknowledging the low number of samples analysed post-treatment, the phenomenon seems similar to that seen in adults and presented in the SmPC. Although the significance of these differences remains uncertain, the MAH agreed to update the *Paediatric population/Description of selected adverse reactions/Immunogenicity in patients with pJIA treated with subcutaneous abatacept* paragraph in SmPC Section 4.8, by including results from each age cohort separately. The labeling revisions will be assessed in detail in context the upcoming post article 46 type II variation.

The MAH also further discussed, as requested, the possible immunogenic effect/adjuvant potential of the silicon contained in the different types of syringes. In the study IM101301, no apparent reason for the higher ADA incidence observed in the 2 to 5-year age cohort could be established. Namely, it could not be established that this difference would in any way be related to the type of syringes or the silicon oil content (same syringe was used in both age cohorts; higher incidence of ADAs in the IV pJIA-study, which did not use siliconized syringes). It is agreed with the MAH that in this study set up undoubtedly uncertainties will remain related to the silicone issue; however, this issue will not be pursued further. However, these findings on immunogenicity in general are considered as valuable information for prescribers, and thus the SmPC should be updated to include this novel information in the upcoming post art. 46 type II variation. In addition, recognising the overall limited information available with respect to immunogenicity, the immunogenicity issue should be further followed by the MAH. Immunogenicity will also be re-evaluated at the 5-year follow-up of Study IM101301 as part of a separate post-authorisation commitment by the date specified in the RMP.

The observations of MLAs of eosinophilia as well as urinary WBC and RBC remain unchanged from the interim report, and although any definitive explanation for the eosinophilia remains elusive, it does not seem to be associated with clinical AEs. The same holds true for the urinary findings. However, the MAH provided an acceptable justification that these findings appear not to be informative to the prescribing physician and do not call for a SmPC revision. In addition, the laboratory findings of MLA values for low blood glucose, elevated creatinine, elevated potassium and low blood leukocytes, in this study population of pJIA patients on SC abatacept treatment, appeared not to represent new safety signals for abatacept and appeared, not to be clinically meaningful to the prescribing physician. Therefore, no update of the SmPC is called for. The MAH presented proposed changes to the PI, which

will be assessed in the post article 46 type II variation. In addition, the MAH is expected to provide the final 5-year follow-up results, with a further discussion on the safety aspects previously identified by the CHMP, as a separate post-authorisation commitment by the date specified in the RMP.

The overall benefit-risk profile of abatacept remains unchanged.

3. Rapporteur's overall conclusion and recommendation

Adequate responses to the all eight questions of the requested "Additional clarification request" have been provided by the MAH (see section 5, "Assessment of MAH responses to the Additional clarification requested").

No additional efficacy or PK data will be collected for the study beyond the 20-month LTE. No new safety signals have been identified and the data reported in this submission are consistent with previously reported data for study IM101301. The Article 46 requirements are considered fulfilled with the present submission; however, the MAH should submit within 60 days a variation to update the PI and the RMP with those new data. The RMP should be updated to state that 2-year results for the study have been submitted. In addition, the MAH is expected to provide the final 5-year follow-up results, with a further discussion on the safety aspects previously identified by the CHMP, as a separate post-authorisation commitment by the date specified in the RMP.

There is no change in the general benefit-risk profile of ORENCIA.

☒ **Fulfilled with follow-up:**

The MAH should submit within 60 days a variation to update the PI and the RMP with the data from the Article 46 submission. The RMP should be updated to state that 2-year results for the study have been submitted. In addition, the MAH is expected to provide the final 5-year follow-up results, with a further discussion on the safety aspects previously identified by the CHMP, as a separate post-authorisation commitment by the date specified in the RMP.

4. Additional clarification requested (in 05/2019)

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH should discuss lack of efficacy, resulting in discontinuation, seen in the current study (IM101301) and compare to previous paediatric studies, particularly study IM101033 using intravenous abatacept. Does the MAH consider the mode of administration of abatacept (SC versus IV) to have any effect on the lack of efficacy observed?

2. Two previously reported infectious SAEs in the paediatric population (varicella and sepsis) are individually identified in Section 4.8 of the current SmPC. As the experience from the 2 - 5 year age cohort still remains very limited, the MAH should discuss whether either or both of the two newly identified SAEs (limb abscess and cellulitis) in this age cohort should also be similarly described or included in the current characterisation.

3. A very high general level of infections throughout the paediatric population was observed in the study, with younger children (2-5 years) being more affected than the older cohort. The MAH should discuss whether further detail concerning infections should be incorporated in the SmPC.

4. The MAH should further discuss the findings of increased eosinophils, white blood cells in urine and increased ADAs in the 2 - 5 year age cohort, and whether these should be described in the SmPC to inform the treating physician. The MAH could consider modifying the

immunogenicity section by including results for both age groups separately, i.e. 2 - 5-year olds and 6 - 17-year olds.

5. The MAH should explain the significance of other frequently observed MLA's identified in the CSR (including low glucose, elevated creatinine and elevated potassium), relating the response to both age cohorts, and discuss whether other frequently observed MLA's should be included in an update to the SmPC.

6. No specific follow-up nor discussion was provided on the possible immunogenic effect/adjuvant potential of the silicon contained in the different types of syringes; the MAH should discuss this, as requested within the variation EMEA/H/C/000701/X/0117/G.

7. Section 5.1. of the SmPC describes 15 patients in the 2 - 5 year age cohort as ongoing in the 2-year period, and this section should be updated within 60 days of finalisation of the Art. 46 process.

8. The RMP should also be updated within 60 days of finalisation of the Art. 46 process to state that the 2-year results have been submitted.

The timetable is a 30-day response timetable with clock stop.

5. Assessment of MAH responses to Additional clarification requested

Question 1

The MAH should discuss lack of efficacy, resulting in discontinuation, seen in the current study (IM101301) and compare to previous paediatric studies, particularly study IM101033 using intravenous abatacept. Does the MAH consider the mode of administration of abatacept (SC versus IV) to have any effect on the lack of efficacy observed?

MAH response

The mode of administration does not appear to have an effect on the efficacy observed; response rates with both IV and SC dosing showed high effectiveness. The most common reason for discontinuation in subcutaneous (SC) Study IM101301 was lack of efficacy (LOE). Subjects from Study IM101301 were stratified by age cohort (2 age cohorts: 2 through 5 year old and 6 through 17 year old) to receive open label (OL) weight- tiered SC abatacept (10 to <25 kg [50 mg], 25 to <50 kg [87.5 mg], ≥ 50 kg [125 mg]) weekly for 24 months. The mean duration of the cumulative period was 22.3 ± 6.21 months for the 2 to 5-year age cohort and 21.8 ± 6.87 months for the 6 to 17 year age cohort, respectively. The incidence of discontinuation due to LOE at Month 4 (time of the primary PK endpoint) and cumulative period was:

<u>*Month 4*</u>: 5 (2.3%) of 219 subjects

-2 through 5 year age cohort: 2 (4.3 %) of 46 subjects

-6 through 17 year age cohort: 3 (1.7%) of 173 subjects

<u>*Cumulative Period*</u>: 22 (10.0%) of 219 subjects

-2 through 5 year age cohort: 5 (10.9%) of 46 subjects

-6 through 17 year age cohort: 17 (9.8%) of 173 subjects

In Study IM101301, the discontinuation rates due to LOE were lower in the older age cohort at Month 4 and similar during the cumulative period.

The abatacept IV study, Study IM101033, had discontinuation rates due to LOE in 3 separate periods due to its randomized, placebo-controlled withdrawal study design:

Period A: 4 month, open-label, lead in period. Subjects were dosed with abatacept 10 mg/kg IV on Days 1, 15, 29 and monthly thereafter. The efficacy endpoint at Month 4 was the ACRp30. A total of 17 (8.9%) of 190 subjects discontinued due to LOE.

Period B: 6 month, randomized, double blind, placebo-controlled withdrawal period. Only ACRp30 responders of Period A at Month 4 could be randomized into Period B. Subjects were dosed with abatacept 10 mg/kg IV on a monthly basis. The efficacy endpoint at Month 6 was the time to flare rate. Discontinuation rates due to LOE were:

-Abatacept: 10 (16.7%) of 60 subjects

-Placebo: 31 (50 %) of 60 subjects

Period C: Open label period for 5 years. A total of 24 (15.7%) of 153 subjects who participated in Period C discontinued due to LOE (as-observed analysis). Subjects who participated in Period C came from 3 cohorts:

-Period A Non-responders: 11 (30.6%) of 36 subjects

-Period B Abatacept-receiving subjects: 5 (8.6%) of 58 subjects

-Period B Placebo-receiving subjects: 8 (13.6%) of 59 subjects

The overall 15.7% discontinuation rate due to LOE observed during Period C is low since the mean duration of Period C was 53.2 ± 21.0 months.

The only relevant direct comparison of discontinuation rates due to LOE between the two studies that can be made is between the initial 4 months of OL abatacept treatment in SC Study IM101301 and Period A (4 months) of IV Study IM101033. The discontinuation rate from LOE was 2.3% (5 of 219 subjects) in the initial 4 months of Study IM101301 and was 8.9% (17 of 190 subjects) in Period A of Study IM101033. The duration of comparison is relatively short (4 months) and these discontinuation rates do not appear to be different enough to draw a definitive conclusion that there is a higher discontinuation rate with administration of IV abatacept.

Other comparisons of the discontinuation rates due to LOE between SC abatacept Study IM101301 and IV abatacept Study IM101033 are confounded by the following issues:

- The subjects in Period B of Study IM101033 are not the same as subjects who enrolled in Study IM101301 because subjects in Period B of Study IM101033 are all responders to 4 months of abatacept treatment (during Period A) before randomization into Period B. Discontinuation rates due to LOE in Period B of Study IM101033 cannot be compared to any discontinuation rate due to LOE from Study IM101301.
- The subjects in Period C of Study IM101033 come from 3 cohorts, including subjects who were non-responders from Period A, placebo-treated subjects from Period B, and subjects who have been treated with abatacept during both Period A (4 months) and Period B (6 months). This population is therefore not comparable to subjects who enrolled in Study IM101301.
- The mean (±SD) duration of exposure to continuous abatacept treatment during the cumulative period in Study IM101301 is shorter than the mean duration of continuous abatacept treatment in Period C (53.2 ± 21.0 months) (Table 6.1A from the IM101033 CSR Addendum 3). Therefore, comparison of the discontinuation rates due to LOE cannot be properly interpreted.

In summary, the clinical response rates to IV abatacept (Study IM101033) and SC abatacept (Study IM101301) were high, indicating that abatacept is highly effective in children with pJIA.

A comparison of the discontinuation rates due to LOE (during the initial 4 months of abatacept treatment) does not suggest that the mode of administration (SC versus IV) of abatacept had an impact on the discontinuation rate due to LOE observed in these two trials during the cumulative period.

Assessment MAH response

The MAH has, as requested, discussed lack of efficacy, resulting in discontinuation, seen in the current SC study (IM101301) and compared it to previous paediatric studies, particularly study IM101033 using intravenous abatacept, to determine whether the mode of administration of abatacept (SC versus IV) may have a possible role in the lack of efficacy reported. Overall, the direct comparison of the two studies is hampered by differences in methodological issues, for example, in the design of the studies and the study populations (in the different phases of the studies). The results from the most applicable period for the comparison, a period of only four months, did not indicate clear difference in lack of efficacy, according to the mode of administration of abatacept. Other comparative analyses were confounded to the extent that relevant interpretations of the data could not be made.

In conclusion, based on the limited data currently available, it can be agreed on with the MAH, that the mode of administration of abatacept (SC versus IV) appeared not to have a significant effect on the lack of efficacy observed. However, the currently available data, namely the available comparative data is scarce and fragmented, therefore, firm conclusion cannot be drawn. Thus, this issue should be revisited when the 5-year follow-up data for the SC study IM101301 becomes available. The MAH is expected and has agreed to provide these data as a separate post-authorisation commitment by the date specified in the RMP.

Conclusions

Issue resolved.

Question 2

Two previously reported infectious SAEs in the paediatric population (varicella and sepsis) are individually identified in Section 4.8 of the current SmPC. As the experience from the 2 - 5 year age cohort still remains very limited, the MAH should discuss whether either or both of the two newly identified SAEs (limb abscess and cellulitis) in this age cohort should also be similarly described or included in the current characterisation.

MAH response

Limb Abscess

One 3-year old patient from the 2 to 5 year age cohort experienced a serious adverse event (SAE) of Abscess limb (right thigh) on Day 666 that was assessed as severe in intensity and related to subcutaneous (SC) abatacept 50 mg weekly. The child was treated with amoxicillin for 6 days and had surgery, with resolution of the event 19 days after. . This was the only event of Abscess (incidence of 2.2%) reported in the 2 through 5 year age cohort (total n= 46).

This patient was not on corticosteroids during the onset of the Abscess, but was on methotrexate (MTX) 10 mg/week from 10-Apr-2017 to 18-Dec-2017. MTX may or may not have contributed to a higher rate of infection in children with pJIA.

Hospitalization for bacterial infections related to skin and soft tissues have been reported in 12% of children with pJIA. However, the literature is scarce with respect to an assessment of abscesses (and infections) in children with pJIA who are 2 through 5 years of age.
Due to the serious nature, severity, relatedness to abatacept, and lack of additional risk factors (other than pJIA) for infection (e.g., corticosteroid use), the MAH agrees to individually describe the limb abscess in the *Paediatric population/Description of selected adverse reactions/Infections* paragraph of

the current Summary of Product Characteristics (SmPC) Section 4.8 (see all proposed labeling revisions to the SmPC Section 4.8 at the end of the response to Question 5).

Cellulitis

One 2-year old patient from the 2 through 5 year age cohort experienced a SAE of Cellulitis (left ankle and thigh) on Day 674 that was assessed as moderate in intensity and not related (based on investigator's judgment) to SC abatacept 50 mg weekly. Next year, fever and skin infection of the left ankle and thigh was resistant to the analgesic metamizole. Cellulitis was then diagnosed. The child was treated with antibiotics; treatment included IV cephalexin, IV clindamycin and oral sulfamethoxazole-trimethoprim and the infection resolved 11 days later. Study drug was interrupted during the event and resumed afterwards.

The incidence of Cellulitis in the 2 through 5 year age cohort in this study is 2.2%.

The MAH assessed that this SAE of cellulitis should not be described in Section 4.8 the SmPC for the following reasons:

1) This child was on concomitant corticosteroid therapy during the onset of cellulitis. Corticosteroids are known to increase the risk for infection in children with pJIA and increase the rate of hospitalized bacterial infections in these children.

2) Therefore, the event is more likely related to concomitant corticosteroid therapy but unlikely related to abatacept use; the MAH does not think that listing this event in the SmPC would provide any relevant information to guide the prescriber.

Table 2-1: Prior and Concomitant Corticosteroid Use for Subject with cellulitis event

	Dose	Start	End	Comment
Meprednisone (methylprednisolone)	2 mg QD	Unknown	14-Dec-2016	
Meprednisone	2 mg every other day	15-Dec-2016	Continued	Infection: 04-Nov-2017 to 15-Dec-2017
Meprednisone	Zero	15-Dec-2017	08-Feb-2018	Infection resolved on 15-Dec-2017

Source: Appendix 4.2.2 of 24-month IM101301 CSR

3) This infection was considered moderate in severity and responded rapidly with antibiotic treatment, even though effective antibiotic treatment had not been administered during the preceding month of the infection (symptoms began on 04-Nov-2017). This shows that the course of response to treatment of the cellulitis was not unusual or unexpected.

Table 2-2: Antibiotic treatment during Hospitalization for Subject with cellulitis event

	Start	End	Comment
Cephalexin	04-Dec-2017	06-Dec-2017	Metamizole (analgesic) started and ended on 04-Dec-2017
Clindamycin	06-Dec-2017	09-Dec-2017	
Sulfamethoxazole-Trimethoprim	10-Dec-2017	15-Dec-2017	Cellulitis resolved on 15-Dec-2017

Source: Appendix 4.2.2 of 24-month IM101301 CSR

Assessment MAH response

As two previously reported infectious SAEs in the paediatric population (varicella and sepsis) are individually identified in Section 4.8 of the current SmPC, the MAH was requested to discuss whether either or both of the two newly identified SAEs (limb abscess and cellulitis) in the 2 - 5 year age cohort should also be similarly described, as experience overall from the 2 - 5 year age cohort still remains very limited.

The MAH has provided the narratives of these two single SAE cases. Based on the data provided, the MAH proposes, that limb abscesses should be individually described in the SmPC Section 4.8. owing to the serious nature, severity and relatedness of this SAE to abatacept treatment, and due to the lack of any additional risk factors (other than pJIA) for infection (for example, corticosteroid use). Overall, this justification can be agreed on.

On the other hand, a single case of cellulitis, deemed a SAE, was reported in a 2-year old pJIA patient. The patient was on concomitant corticosteroid treatment (an acknowledged risk factor for infections) at the time of onset of the infection. The cellulitis was, based on investigator's judgment, not related to the SC abatacept therapy (evidence of causality was not evident) and considered most likely to be related to the concomitant corticosteroid treatment. The infection was moderate in severity and responded rapidly to antibiotic treatment. Overall, the clinical course and response to treatment was considered not to be unusual or unexpected. Thus, the overall available data on this single SAE of cellulitis does not justify a description in section 4.8 the SmPC.

Conclusions

Issue resolved.

Question 3

A very high general level of infections throughout the paediatric population was observed in the study, with younger children (2-5 years) being more affected than the older cohort. The MAH should discuss whether further detail concerning infections should be incorporated in the SmPC.

MAH response

A response to the EMA regarding the higher incidence of infections in the 2 through 5 year age cohort compared to the 6 through 17 year age cohort in SC Study IM101301 was submitted on 12-Oct-2018 (response to Question #14 of the Day 120 List of Questions in procedure *EMEA/H/C/000701/X/0117/G*). The higher incidence of infection in the younger age cohort was due to a higher incidence of upper respiratory tract infections, which is seen in very young children. The EMA requested that a comparative analysis be performed once the 2 through 5 year age cohort (n = 46) had completed the cumulative period of Study IM101301.

Forty (87.0%) of 46 subjects in the 2 through 5 year age cohort were reported to have an infection during the cumulative period compared to 118 (68.2%) of 173 subjects in the 6 through 17 year age cohort (Supplemental Table S.6.34 of the 24-month IM101301 CSR and Supplemental Table S.6.4 of January 2018 CSR). The incidence rate (confidence interval) for infections in the 2 through 5 year age cohort (n = 40) during the cumulative period was 164.97 (121.01, 224.91) per 100 person-years (Table S.6.34 of the 24-month IM101301 CSR). The incidence rate (confidence interval) for infections in the 6 through 17 year old cohort (n = 118) during the cumulative period was 79.81 (66.64, 95.59) per 100 person-years.

2 Through 5 Year Age Cohort

In the 2 through 5 year age cohort, the most commonly reported infections were infections of the upper respiratory tract: Nasopharyngitis (17 subjects, 37.0%), Upper respiratory tract infection (10 subjects, 21.7%), Rhinitis (8 subjects, 17.4%), and Pharyngitis (6 subjects, 13.0%) (Table S.6.14 of 24-month IM101301 CSR). Most subjects had single occurrences of an infection (Supplemental Table S.6.45 of 24-month IM101301 CSR). Six subjects (13.0%) experienced 2 to non-serious occurrences of Nasopharyngitis, and 4 subjects (8.7%) experienced at least 4 non-serious occurrences of Nasopharyngitis (Supplemental Table S.6.45 of 24-month IM101301 CSR).

The most common upper respiratory infections (> 10%) that were related to study drug included Nasopharyngitis (11 subjects, 23.9%), Upper respiratory tract infection (6 subjects, 13.0%), and Rhinitis (5 subjects, 10.9%).

All infections were mild to moderate except for an infection reported for one Subject (Limb abscess) (See Response to Question 2). One subject discontinued the study due to AEs of Pyrexia, Rhinitis, and Cough.

Two (4.3%) of the 46 children in the 2 through 5 year age cohort were reported with serious infections (Limb abscess and Cellulitis).

All infections were reported to have resolved during the cumulative period except in two subjects with molluscum contagiosum (onset on Day 722 for one subject and onset on Day 197 for the other). Both AEs were mild, not related to study drug, and did not result in either interruption or discontinuation of abatacept.

6 Through 17 Year Age Cohort

In the 6 through 17 year age cohort, the most commonly reported infections during the cumulative period (based on 152 subjects with AEs) were infections of the upper respiratory tract: Nasopharyngitis (52 subjects, 30.1%) and Upper respiratory tract infection (32 subjects, 18.5%).

The most common upper respiratory infections (> 10%) that were related to study drug included Nasopharyngitis (23 subjects, 13.3%) and Upper respiratory tract infection (8 subjects, 4.6%) (Table S.10 of January 2018 CSR).

All infections were of mild or moderate intensity, except for 1 case of Sepsis that was severe in intensity. The subject who experienced Sepsis discontinued from the study.

Four subjects from the 6 through 17 year age cohort were reported with a serious infection (one subject with Appendicitis, one subject with Pneumonia, one subject with Pyelonephritis, and one subject with Sepsis).

All infections were reported to have resolved during the cumulative period except in 3 subjects: one with Nasopharyngitis onset on Day 26, one with Bronchitis onset on Day 721, and one with Fungal mycosis onset on Day 459. All cases were mild and only the Bronchitis was felt to be related to study drug. None of the infections resulted in interruption or discontinuation of abatacept. The resolution of Sinusitis (Day 467 onset) was reported as unknown.

Summary

The percentage of infections was higher in the 2 through 5 year age cohort (87.0%) than the 6 through 17 year age cohort (68.2%), mostly because of the higher incidence of upper respiratory airway infections during the cumulative period. This result is similar to that observed in the previous response to Question #14 of the Day 120 List of Questions of EMEA/H/C/000701/X/0117/G procedure submitted on 12-Oct-2018. All infections in both age cohorts were mild to moderate except 1 infection reported in a subject in the 2 through 5 year age cohort (Severe limb abscess) and 1 infection

reported in a subject in the 6 through 17 year age cohort (Sepsis). Serious infections were infrequent in both age cohorts. All infections were reported to have resolved except for Molluscum Contagiosum in two children in the 2 through 5 year old cohort and Nasopharyngitis, Bronchitis and Fungal Mycosis, respectively, in 3 children in the 6 through 17 year old cohort.

The higher incidence of upper respiratory airway infections is consistent with the literature; upper respiratory infections (involving the ear, nose, and throat) are the most common pathology in children 6 months to 6 years of age. Children less than 6 years of age also have a high prevalence of infections due to recurrent respiratory infections from their exposure to other children through attendance at day care and exposure to new pathogens.

Reflective of the observed higher incidence, the MAH agrees to add text to the SmPC that a higher incidence of infection (87.0% vs 68.2%) (mostly upper respiratory tract infections) was reported in younger children with pJIA (2 through 5 years old) treated with SC abatacept compared to older children with pJIA (6 through 17 years old) (see proposed labeling revisions to the SmPC Section 4.8 at the end of the response to Question 5).

Assessment MAH response

A very high general level of infections throughout the paediatric population was observed in the Study IM101301, with the younger children (2-5 years) being more affected than children in the older cohort (6-17 years). This was already evident on incomplete data sets of the interim analysis, and thus on request, a comparative analysis was reiterated on the full data sets, when the 2 to 5-year old age cohort (n = 46) had completed the cumulative period.

In line with the previous data, in both age groups, the overall number of infections remained high, with the younger children being more affected. This was mainly due to a higher incidence of upper respiratory infections in the cumulative period. All infections in both age cohorts were mild to moderate, excepting a sole severe limb abscess in the younger age cohort and a single case of sepsis in the older age group. Serious infections were infrequent in both age cohorts. All infections were reported to have resolved, except for *molluscum contagiosum* in two children in the 2 to 5 year old cohort and nasopharyngitis, bronchitis and fungal mycosis, respectively, in 3 children in the 6 to 17 year old cohort.

In line with these data, the MAH agrees to add a text to the SmPC stating that a higher incidence of infection (87.0% vs 68.2%), mostly upper respiratory tract infections, was reported in younger children with pJIA (2 to 5-year old) treated with SC abatacept compared to older children with pJIA (6 to 17-year old). The proposed text revisions to the SmPC Section 4.8 are currently already presented at the end of the response to Question 5, but will be assessed in detail in context of the post Article 46 type II variation.

Conclusions

Issue resolved.

Question 4

The MAH should further discuss the findings of increased eosinophils, white blood cells in urine and increased ADAs in the 2 - 5 year age cohort, and whether these should be described in the SmPC to inform the treating physician. The MAH could consider modifying the immunogenicity section by including results for both age groups separately, i.e. 2 - 5-year olds and 6 - 17-year olds.

MAH response

Increased Eosinophils in the 2 Through 5 Year Age Cohort

A response to the EMA regarding increased eosinophils in the 2 through 5 year age cohort was submitted on 12-Oct-2018 (response to Question #16 of the Day 120 List of Questions in procedure *EMEA/H/C/000701/X/0117/G*). Of the 46 subjects in the 2 through 5 year age cohort with pJIA, 12 (26.1%) met the pre-specified Marked Laboratory Abnormality (MLA) threshold for eosinophils (0.75 x 10^3 cells/µL) during the cumulative treatment period. Of the 12 subjects who met the MLA threshold for eosinophils, 3 (25.0%) had an AE within ± 21 days of the reported MLA value: Rhinitis, Influenza and Conjunctivitis (Table 16-1 in the EMA Response to Question #16). The window for inflammatory mediators to enhance the survival of eosinophils is up to 2 weeks; a conservative 21-day window from the day of the MLA for eosinophils was used to capture any AEs that may have been missed at the time the eosinophilia was documented. Most of these MLAs were isolated and/or intermittent findings in this study. Fifteen of the 46 subjects had not completed the full 24 months of abatacept treatment at the time of the January 2018 IM101301 CSR data lock.

The 24-month IM101301 CSR has 2-year data on all 46 subjects from the 2 through 5 year age cohort. Fourteen (30.4%) of the 46 subjects in this age cohort met the threshold for MLA for eosinophils (Table 6.3.7-1 and Appendix 7.2.2 of the 24-month IM101301 CSR). Two subjects were not previously reported in the above-mentioned Response to Day 120 Question #16. One Subject had MLA values on Days 478, 646, and 730, and an AE of Hand-foot-and- mouth disease (not associated with eosinophilia) was reported on Day 725. One Subject had an isolated MLA value on Day 728; this was not associated with an AE. Neither of these two subjects had a prior medical history that could potentially be associated with eosinophilia.

One Subject had a MLA value of high eosinophils on Day 417 and was also reported with an anti-CTLA4 abatacept antibody; however this antibody occurred 168 days after Day 729 (Month 24).

Summary

The EMA Response submitted on 12-Oct-2018 did not find a definitive cause for many of the reported MLAs for high eosinophils; many of these values were isolated and/or intermittent during the cumulative period. A high incidence of upper respiratory infection in the 2 through 5 year age cohort is expected and was observed during the cumulative period of the study. Viruses such as rhinovirus and respiratory syncytial virus are very common infections in young patients and can be associated with eosinophilia. Few AEs (Rhinitis, Influenza, and Conjunctivitis) were reported that could be associated with an increased level of eosinophils; since the EMA Response, 2 additional subjects were reported to have MLA values of elevated eosinophils, but did not have AEs known to be associated with increased eosinophils. Seasonal allergies may have also played a contributing role for eosinophilia in this global trial; 5 subjects with MLA values of elevated eosinophils from the 2 through 5 year age cohort used concomitant respiratory medications (including antihistamines, anti-asthmatic, and nasal, cough and cold, and throat preparations) during the cumulative period. Due to the transient and/or isolated MLA values of elevated eosinophils, the multiple, potential etiologies for increased eosinophils in this age group, and lack of meaningful association of increased MLA values of eosinophils during treatment with abatacept, the MAH assessed that this finding is not informative to the prescribing physician and therefore, should not be included in the SmPC.

Increased White Blood Cells in the Urine in the 2 Through 5 Year Age Cohort

A response to the EMA regarding increased urine WBCs in the 2 through 5 year age cohort was submitted on 12-Oct-2018 (response to Question #15 of the Day 120 List of Questions in procedure *EMEA/H/C/000701/X/0117/G*). A total of 8 of 25 (32.0%) subjects with pJIA from this age cohort were reported with a MLA threshold for increased urine WBCs. Most of the MLAs were transient

(Appendix 15.2 and Appendix 15.3 of the January 2018 CSR), not associated with an AE (both AEs associated with the urinary tract [e.g., urinary tract infections] and AEs outside of the urinary tract [e.g., gastroenteritis and vaginal inflammation]), and did not appear to be clinically meaningful.

In the 2 through 5 year age cohort, as reported in the 24-month IM101301 CSR, 10 (35.7%) of the 28 subjects met the MLA threshold for increased urine WBCs (Table 6.3.7-1 of 24-month IM101301 CSR). The 2 additional subjects with increased urinary WBCs not previously reported in the above mentioned Response to Day 120 Question #5 were Subject IM101301-31-227 and Subject IM101301-50-228; both had solitary MLA values. During the 24-month cumulative period, 9 of the 10 subjects had a single MLA value; only Subject IM101301-60-168 had a MLA value on the same day (Day 197) as an AE (Urinary tract infection) (Appendix 7.2.2 of 24-month IM101301 CSR). Three additional subjects in the 2 through 5 year age cohort had AEs that could be associated with increased urinary WBCs (Subject IM101301-14-125 with Gastroenteritis, Subject IM101301-31-227 with Urinary tract infection, and Subject IM101301-44-214 with Gastroenteritis) but the single urinary WBC MLA value did not correspond at all to the onset of the respective AE (Appendix 6.2.2 and Appendix 7.7.2 of 24-month IM101301 CSR). Pyuria was also not reported as an AE in the 2 through 5 year age cohort.

Summary

Overall, the increase in urinary WBCs that met the MLA threshold in the 2 through 5 year age cohort were mostly solitary findings and not associated with an AE except for in 1 subject. These findings do not appear to be clinically meaningful and are not informative to the prescribing physician. Therefore, the MAH assessed that modification of the SmPC with the increase in urinary WBCs is not needed.

Immunogenicity Results

Although the significance of the immunogenicity results are uncertain, the MAH agrees to update the *Paediatric population/Description of selected adverse reactions/Immunogenicity in patients with pJIA treated with subcutaneous abatacept* paragraph in SmPC Section 4.8 by including results from each age cohort separately, if this is considered valuable information for prescribers.

The labeling revisions that would be proposed in the context of the upcoming type II variation are provided at the end of the response to Question 5.

Assessment MAH response

The MAH was requested to further discuss the findings of increased eosinophils, white blood cells in urine and increased ADAs in the 2 - 5 year age cohort, and discuss whether these should be described in the SmPC to inform the treating physician.

Increased eosinophils: As requested, the MAH further discussed the findings of increased eosinophils. In the interim assessment, no definitive cause for many of the reported MLAs for high eosinophils were found. Many of the values were isolated and/or intermittent during the cumulative period. Only few AEs (rhinitis, influenza and conjunctivitis) were reported that could be associated with an increased level of eosinophils. Since this assessment, at the 24-months follow-up, the two additional subjects were found to have MLA values of elevated eosinophils, but reported no AEs known to be associated with increased eosinophils. These subjects appeared to have narratives similar to previous data from the interim analyses. Thus, the data accrued, to date, remains with uncertainties. Overall, MLA values of elevated eosinophils appear indeed isolated and/or transient in nature, the possible etiologies are multiple and largely no meaningful associations could be found. Therefore, it can be agreed with the MAH that due to the nature of this finding it appears not to be informative to the prescribing physician and does not call for a SmPC revision.

WBC in urine: In the interim analyses, in the 2 to 5 year age cohort of subjects with pJIA, a finding of increased urine WBCs surpassing the MLA threshold was seen. Most of the MLAs were solitary cases

and transient, they were not clearly associated with an AE and were deemed not to be clinically meaningful. Since then, at the 24-months follow-up, two additional subjects tested with increased urinary WBCs not previously reported, both with single occurrences of the MLA test results. Three pJIA patients had AEs that could have been be associated with an increased urinary WBC MLA value, but the single value did not correspond to the onset of the respective AE. Pyuria was not reported as an AE in this younger age group. Thus, overall, data from the two additional patients appear in line with the results of the interim assessment, were this finding of WBC MLA appeared not clinically meaningful enough or informative enough to the physician to merit a SmPC amendment.

Immunogenicity: although the significance of a higher rate of ADAs in the younger age group of pJIA patients remains uncertain, the data are deemed as valuable information for prescribers, and thus results from each age cohort should be described in the SmPC separately. The MAH agrees to update the immunogenicity text on patients with pJIA treated with subcutaneous abatacept in SmPC Section 4.8 in the upcoming post art. 46 type II variation.

Conclusions

Issue resolved.

Question 5

The MAH should explain the significance of other frequently observed MLA's identified in the CSR (including low glucose, elevated creatinine and elevated potassium), relating the response to both age cohorts, and discuss whether other frequently observed MLA's should be included in an update to the SmPC.

MAH response

The threshold for the Marked Laboratory Abnormality (MLA) values for all laboratory tests are listed in Appendix 7.2.2 of the 24-month IM101301 CSR. These thresholds apply to both the 2 through 5 year age cohort and the 6 through 17 year age cohort. The MLA thresholds for low glucose, elevated creatinine, and elevated potassium are as follows:

- Low (serum) glucose: < 65 mg/dL
- Elevated creatinine: > 1.5X Pre-treatment
- Elevated potassium: < 0.9X lower limit of normal (LLN) or > 1.1X upper limit of normal (ULN), or if Pre-treatment < LLN then use < 0.9X Pre-treatment or > ULN, or if Pre-treatment > ULN then use > 1.1X Pre-treatment or < LLN

A conservative window of 30 days before or after the occurrence of a MLA value was used to determine the association of the MLA value to any adverse event (AE).

<u>Low Glucose</u>

2 Through 5 Year Age Cohort

In the 2 through 5 year age cohort, 10 (21.7%) of the 46 subjects were reported with a MLA value for low serum glucose during the cumulative period (Table S.7.3 of the 24-month IM101301 CSR). Eight of these 10 children had only a single MLA value of low glucose during the 24-month cumulative period, with normal glucose values at study visits before and after the MLA value. Two children (two subjects and) had two episodes of MLA values; one subject had the lowest MLA value among all 10 children in this age cohort. There did not appear to be any trend for the onset of these MLA values; they occurred any time between Day 28 to Day 486. One subject had tonsillitis and constipation within 30 days of the MLA value.

None of the MLA values among these 10 subjects were associated with AEs or symptoms that could be associated with hypoglycemia (eg, syncope, lightheadedness, and headache) (Appendix 6.11.2 of 24-month IM101301 CSR). In addition, none of these 10 subjects were treated for the MLA value (Appendix 4.2.2) and none had pre-existing diabetes (Appendix 3.3.2).

6 Through 17 Year Age Cohort

In the 6 through 17 year age cohort, 36 (20.9%) of the 172 subjects were reported with a MLA value for low serum glucose during the cumulative period (Table 7.3.7-1 of the January 2018 IM101301 CSR). Of these 36 subjects, 32 had a single MLA value of low glucose during the 24-month cumulative period, with normal glucose values at study visits immediately before and after the MLA value; 2 subjects had 2 episodes of MLA values, and 2 other children had 3 episodes of MLA values.

One subject had eczema, one subject had proteinuria and one subject had Episcleritis, Respiratory Tract Infection and Limb Abscess within 30 days of the MLA value.

There did not appear to be any trend for the onset of these MLA values; they occurred any time between Day 28 to Day 729. Two children had the lowest MLA values for glucose (40 mg/dL) during the cumulative study that were solitary values, were not associated with an AE, and did not require treatment.

None of the MLA values for low glucose in the 36 children in the 6 through 17 year age cohort had AEs that can be attributed to hypoglycemia (e.g., Syncope, Lightheadedness, Headache) within 30 days of the MLA value (Appendix 6.11.1) except for one subject who was reported with vertigo on Day 36 following an MLA glucose value of 61 mg/dL on Day 23. However, the baseline and Day 57 MLA values were 121 mg/dL and 83 mg/dL, respectively, and the event of Vertigo was not related to abatacept (based on investigator judgment). None of the MLA values in these 36 children required treatment.

None of the children in Study IM101301 had a past medical history of diabetes; one subject was taking metformin (for polycystic kidney disease) and did not have a MLA value of low glucose during the cumulative period.

Summary

Hypoglycemia in children is most often associated with the use of insulin or hypoglycemic agents; however, only 1 child was taking a hypoglycemic agent (metformin) and did not have a MLA value for low glucose (Appendix 3.3.1 and Appendix 7.2.1 of the January 2018 IM101301 CSR). Other causes for hypoglycemia include a missed meal, prolonged fasting, strenuous exercise, diarrhea or vomiting, and illness. The majority of the MLA values for low glucose were solitary values in most of subjects in the 2 through 5 and 6 through 17 year age cohorts who experienced a MLA value. There was no trend in the onset of the MLA values. None of the MLA values could be attributed to an AE that clinically would be associated with hypoglycemia (within 30 days before or after the MLA value) during the 24-month cumulative period, including the few subjects who had multiple MLA values. None of the subjects with MLA values in the 2 through 5 year age cohort nor in the 6 through 17 year age cohort required treatment for the low glucose levels, including 2 children who had the lowest MLA glucose values (40 mg/dL). No subject discontinued the study due to an AE associated with low glucose MLA value (Section 6.3.4 of the 24-month IM101301 CSR).

Overall, these low glucose MLA values are not clinically meaningful and do not represent a new safety signal for abatacept. The MAH assessed that the SmPC should not be modified to include information on the low glucose MLA values observed in subjects with pJIA treated with abatacept.

Elevated Creatinine

2 Through 5 Year Age Cohort

In the 2 through 5 year age cohort, 7 (15.2%) of the 46 subjects were reported with a MLA value for elevated serum creatinine during the cumulative period (Table S.7.3 of the 24-month IM101301 CSR). Of these 7 subjects, 4 Subjects had a single MLA value of elevated creatinine during the 24-month cumulative period. All 4 subjects had normal creatinine values at study visits before and after the MLA value (Appendix 7.2.2 of the 24-month IM101301 CSR). Two children had 2 episodes of MLA values, and 1 child had more than 2 episodes of MLA values (Appendix 7.2.2 of the 24-month IM101301 CSR and Table 5-3).

Table 5-3: 2 Through 5 Year Old Subjects with Multiple MLA Values for Elevated Creatinine* During Cumulative Period

Subject	Day (D) of MLA	AE within 30 days of the MLA value
Subject 1	29	Psychomotor hyperactivity (D29)
	475	None (Influenza on D414)
	561	None
	638	Pyrexia (D631)
Subject 2	105	Viral rash (D78), Allergic rhinitis (D78)
	650	Varicella (D628)
Subject 3	391	Scleritis (D380), Rash (D380)
	476	Acne (D442)

Although 2 Subjects had multiple MLA values for elevated creatinine, all of the MLA values were still within the normal range for their age. One Subject has a single MLA value on Day 475 that was above the age-adjusted normal range for creatinine, but the MLA value at the next study visit (Day 561) was in the normal age-adjusted range.

In the 2 through 5 year age cohort, 6 of the 7 subjects reported with MLA values for elevated creatinine had normal creatinine levels at the end of the 24 month cumulative period; one Subject had an MLA value at Day 650 but it was still within the normal range (Table 5-4).

None of the 7 subjects with a MLA value for elevated creatinine had a past history of renal disease nor an AE that could be associated with renal disease within 30 days of the MLA.

6 Through 17 Year Age Cohort

In the 6 through 17 year age cohort, 6 (3.5%) of the 172 subjects were reported with a MLA value for elevated serum creatinine during the cumulative period.

Of these 6 subjects, 3 Subjects

had a single MLA value of elevated creatinine during the 24 month cumulative period; all 3 subjects had normal creatinine values at study visits before and after the MLA value. Three subjects had more than a single MLA creatinine value during the cumulative period.

Table 5-4: 6-17 Year Old Subjects with Multiple MLA Values for Elevated Creatinine* During Cumulative Period

Subject	Day (D) of MLA	AE within 30 days of the MLA value
Subject A	308	None
	471	None
Subject B	29	Abdominal pain (D2)
	56	Skin hypopigmentation (D47)
	85	None
	113	Nasopharyngitis (D112)
	197	Abnormal loss of weight (D228)
	309	None
	393	Influenza (D404)
	477	Upper respiratory tract infection (D470)
	554	Upper respiratory tract infection (D554)
	639	Sinusitis (D646)
	728	Asthma (D699)
Subject C	57	None
	183	None
	559	None
	644	None

Although 2 subjects had multiple MLA values for elevated creatinine, all of the MLA values were still within the normal reference range for their age. One subject had a MLA creatinine value on Day 308 that exceeded the normal reference range, but the MLA value returned to a normal creatinine value (0.48 mg/dL) at the following study visit (Day 391).

Two subjects with multiple MLA values had an elevated MLA creatinine value at the end of the cumulative period but these MLA values were still within the normal reference range for age-adjusted creatinine. One subject , who had multiple MLA values, had a normal creatinine value at the end of the cumulative period.

There was no AE that could be associated with renal disease within 30 days of any of the MLA values in the 6 children with MLA values for elevated creatinine. In addition, none of these 6 children had a past medical history of any renal disease.

Summary

In the 2 through 5 year age cohort, 7 (15.2%) subjects had MLA values of elevated creatinine. All of the single MLA values had resolved to normal values by the next study visit. All 7 children from the 2 through 5 year age cohort had normal creatinine values (by the central laboratory reference range for age-adjusted creatinine) at the end of the 24-month cumulative period.

In the 6 through 17 year age cohort, 6 (3.5%) subjects had MLA values of elevated creatinine. MLA values of 3 of the 6 subjects who had a single MLA value returned to normal values by the next study

visit. Two of 3 of these subjects with multiple MLA values had a MLA value at the end of the 24-month cumulative treatment, but these were within the age-adjusted normal reference range for creatinine.

Overall, the elevated creatinine MLA values are predominantly solitary values. For those subjects in both age cohorts with multiple MLA values, the values were virtually all within the normal creatinine reference range (adjusted for their age). None of these MLA values for elevated creatinine was temporally associated with an AE. Therefore, these MLA values are not clinically meaningful to the prescribing physician and do not represent a new safety signal for abatacept. The MAH assessed that the SmPC should not be modified to include information on the elevated creatinine MLA values observed in the children with pJIA treated with abatacept.

Elevated Potassium

2 Through 5 Year Age Cohort

In the 2 through 5 year age cohort, 4 (8.7%) of 46 subjects were reported with a MLA value for elevated potassium during the cumulative period (Table S.7.3 of the 24-month IM101301 CSR). All 4 subjects had a single MLA value for elevated potassium during the 24-month cumulative period; no treatment for hyperkalemia (e.g., insulin, diuretic) was initiated and all MLA values returned to normal at the following study visit (Appendix 4.2.2 and Appendix 7.2.2 of the 24-month IM101301 CSR). None of these values was linked to an AE associated with hyperkalemia (within 30 days of the MLA value).

6 Through 17 Year Age Cohort

In the 6 through 17 year age cohort, 4 (2.3%) of the 172 subjects had an elevated potassium level reported during the cumulative period (Table 7.3.7-1 of the January 2018 IM101301 CSR). All 4 of these subjects had a single MLA value for elevated potassium during the 24-month cumulative period; no treatment for hyperkalemia was initiated and all MLA values returned to normal at the following study visit (Appendix 4.2.1 and Appendix 7.2.1). None of these values were linked to an AE associated with hyperkalemia (within 30 days of the MLA value).

Summary

The MLA values for elevated potassium were solitary in both age cohorts, and were not associated with an AE. No treatment was initiated for the elevated potassium levels, suggesting that these MLA values were of no clinical significance. Overall, the MAH assessed that the SmPC should not be modified to include information on the elevated potassium MLA values observed in the children with pJIA treated with abatacept.

Low Leukocytes

Although the MLA values for low leukocytes were infrequent (6.5%) during the cumulative study period in SC Study IM101301, it is relevant to comment on this infrequent MLA value, since low leukocytes may predispose to serious bacterial infections.

2 Through 5 Year Age Cohort

In the 2 through 5 year age cohort, 3 (6.5%) of the 46 subjects were reported with MLA values for low leukocytes during the cumulative period (Table S.7.3 of the 24-month IM101301 CSR). The MLA values for low leukocytes for all 3 subjects were solitary and resolved to normal values by the next study visit. All infections associated with each subject during the cumulative period are shown in Table 5-5.

Table 5-5: 2 Through 5 Year Old Subjects with MLA Values for Low Leukocytes* During the Cumulative Period

Subject			Day (D) of MLA		All Infections During the Cumulative Period		
					Infection	Related to Study Drug	Intensity
Subject a			110		Pharyngitis (D77)	Yes	Mild
					Nasopharyngitis (D84)	No	Mild
					Rhinitis (D391)	Yes	Moderate
					Rhinitis (D462)	Yes	Moderate
					Rhinitis (D568	Yes	Moderate
Subject b			324		Viral rash (D78)	No	Mild
					Nasopharyngitis (D310)	No	Mild
					Varicella (D628)	No	Mild
Subject c			84		Nasopharyngitis (D233)	Yes	Mild
					Nasopharyngitis (D308)	Yes	Moderate

Nasopharyngitis was reported 26 and 14 days prior to the low leukocyte count in Subjects and, respectively; however no antibiotics were administered for these infections (Subject received clarithromycin prior to Day 1) and neither subject discontinued the study due to Nasopharyngitis (Appendix 4.4.2 and Appendix 6.11.2). None of the infections were serious and all infections were mild to moderate; all of the infections resolved.

6 Through 17 Year Age Cohort

There were no cases of low leukocytes reported in this age cohort.

Summary

The majority of subjects in the 2 through 5-year age cohort with infections during the cumulative period did not have MLA values for low leukocytes (Appendix 7.2.2). Infections in the 3 subjects in the 2 through 5 year age cohort with MLA values for low leukocytes were not serious, were mild to moderate in intensity and did not require antibiotic therapy. The duration between the onset of an infection and the MLA values for low leukocytes also make their association less likely. The MAH assessed that the SmPC should not be modified to include information on the observations of low leukocytes in subjects from the 2 through 5 year age cohort treated with abatacept.

The MAH proposed text revisions to Section 4.8 of the SmPC . However, the updated SmPC will be part of the type II variation to be submitted within 60 days after completion of this Article 46 procedure (P46 064).

Assessment MAH response

The MAH was requested to explain the significance of other frequently observed Marked Laboratory Abnormalities (MLAs) in study IM101301 (including low glucose, elevated creatinine and elevated potassium), relating the response to both age cohorts, and was further requested to discuss whether other frequently observed MLA's should be included in an update to the SmPC. Overall, the thresholds for the MLAs were prespecified and a window of 30 days before or after the occurrence of a MLA value was used to determine the association of the MLA value to any adverse event (AE).

Low blood glucose

In both age groups, the majority of the MLA values for low glucose, during the cumulative period, were single occurrences. The frequencies were similar between the age groups, being 21,7% in the younger and 20,9 % in the older age group. Only a few subjects had multiple values during the 24-month cumulative period. None of these MLA values could be ascribed to any AE or symptoms possibly associated with hypoglycemia. Furthermore, none of the pJIA patients on abatacept treatment required or received treatment for the low blood glucose levels. Moreover, etiologies or any possible trends, of these MLA values for low blood glucose were, overall, not clearly evident. Only one patient was treated with a hypoglycemic medicinal product (metformin), but no laboratory result showed MLA for low blood glucose. In all, no history of diabetes was reported in the study population. Overall, in both age groups the MLA for low blood glucose values appeared not to represent a clinically meaningful safety signal meriting labelling changes.

Elevated creatinine

Elevated creatinine MLA values were more often found in pJIA patients on SC abatacept treatment in the younger age cohort (15.2%), in comparison to pJIA patients in the older age cohort (3.5%). The reason for this difference was not apparent from the provided data. No evidence of causality was evident. Overall, in both age groups the elevated creatinine MLA values were mostly single occurrence and returned to reference values by the next study visit. None of these MLA values for elevated creatinine was associated with an AE. All seven children in the younger age group with elevated creatinine MLA values had age adjusted creatinine values within the reference range at the end of the 24-month cumulative period. For subjects in both age cohorts with multiple MLA values, the values were also almost all within the normal creatinine reference range adjusted for their age. Thus, an elevated creatinine MLA values appears not to be a new safety signal for abatacept in this study group of pJIA patients on SC abatacept treatment and thus appears not to be clinically meaningful to the prescribing physician.

Elevated Potassium

The test results for elevated potassium surpassing the MLA criteria were single occurrences in both age cohorts. They normalized by the following study visit and were not associated with any AEs or symptoms. No treatment was required or initiated for the pJIA patients with elevated potassium levels. Thus, overall, the elevated potassium MLA values observed in both age cohorts of children with pJIA treated with abatacept appear not to be clinically significant.

Low blood leukocytes

Although the MLA values for low leukocytes were infrequent (6.5%) during the cumulative study period in SC Study IM101301, the MAH considered it relevant to comment on this infrequent MLA value, since low leukocytes may predispose to serious bacterial infections.

The majority of subjects with infections, in the younger cohort, during the cumulative period did not have MLA values for low leukocytes. Infections in the three subjects in this cohort, with MLA values for low leukocytes were not serious, were mild to moderate in intensity and did not require antibiotic therapy. According to the MAH, duration between the onset of an infection and the MLA values for low leukocytes also make their association not likely. Thus, it is agreed with the MAH that the SmPC should not be amended on the available data on low leukocytes in subjects from the 2 to 5 year age cohort treated with abatacept. No cases of low blood leukocytes were reported in the older 6 to 17 age group.

Overall Conclusions

Overall, the findings of MLA values for low blood glucose, elevated creatinine, elevated potassium and low blood leukocytes, in this study population of pJIA patients on SC abatacept treatment, do not appear to represent new safety signals for abatacept and thus appear not to be clinically meaningful to the prescribing physician. Therefore, no update of the SmPC is called for.

Issue resolved.

Question 6

No specific follow-up nor discussion was provided on the possible immunogenic effect/adjuvant potential of the silicon contained in the different types of syringes; the MAH should discuss this, as requested within the variation EMEA/H/C/000701/X/0117/G.

Applicant's response

This topic was discussed in the context of procedure EMEA/H/C/000701/X/0117/G, respectively at Day 120 (Question 27) and at Day 180 (Post-Authorisation Measure Question) and the key elements are summarized and consolidated in this response, as requested.

In the previous responses, the MAH discussed the concern of a potential impact of the silicon oil on immunogenicity (IMG), and the quality measures taken to avoid such impact by adding poloxamer 188 to the formulation. The effectiveness of the measures was supported by the results of quality controls on aggregation and available long-term stability data.

From a clinical standpoint, at the time of the January 2018 IM101301 CSR, there was no measurable clinical impact (no associated effects on PK, loss of efficacy, or occurrence of AEs), in patients with Anti-Drug Antibodies (ADAs) in the 2 through 5 year age cohort (as for any other studied population). As part of procedure EMEA/H/C/000701/X/0117/G, the RMP was updated (Version 25.2) to include "Immunogenicity in paediatric patients" as missing information, while awaiting the full data on the 2 through 5 year age cohort.

In Study IM101301 24-month CSR, the ADA frequency was higher in the 2 through 5 year age cohort on-treatment (10.9% versus 2.3% in the older group), and especially in the post-treatment phase (37.5% versus 13.6% in the older group). However, there is no reason to suspect that this difference would be related to the type of syringe (or silicone oil content), as the same type of syringes were used across the study population in Study IM101301 (with lower volumes, hence lower overall exposure to the silicone of the barrel, for lower strengths). Although it may not be appropriate to make indirect comparisons of IMG data across these studies, it is reassuring to note that, the incidence of IMG in Study IM101301 (6.9% of all subjects were seropositive at least once in p JIA SC Study IM101301) are lower than those observed in pJIA IV Study IM101033 (23.3% of subjects were seropositive at least once in pJIA IV Study IM101033 which didn't use siliconized syringes). Consistent with the overall clinical experience with abatacept, no associated effects on PK, loss of efficacy, or occurrence of AEs were identified in relation to IMG results in the 24-month CSR. In conclusion, there is no clear basis to suspect that the higher incidence of IMG observed in the 2 through 5-year age cohort would be related to the type of syringes, no available evidence to further explore this hypothesis, and no evidence for a measurable clinical impact of ADA.

Although the significance of these results is uncertain, the MAH agrees to present the data in the SmPC and to update the corresponding IMG section accordingly, if this is considered valuable information for prescribers (see response to Question 5).

Assessment MAH response

The MAH has as requested, further discussed the possible immunogenic effect/adjuvant potential of the silicon contained in the different types of syringes. The immunogenicity results of the 24-month follow-up of Study IM101301 appear consistent with the initially reported results of the interim analysis. Although the ADA frequency continued to be higher in the 2 to 5 year age cohort under treatment (10.9% versus 2.3% in the older group), and especially in the post-treatment phase (37.5% versus 13.6% in the older group), no clinically meaningful associations with PK, loss of efficacy, or occurrence of AEs were found. In this study IM101301, no clearly apparent reason for the higher ADA incidence observed in the 2 to 5-year age cohort could be established; and namely, no clear evidence could be detected that this difference would in any way be related to the type of syringes or the silicon oil content (same syringe was used in both age cohorts; higher incidence of ADAs in the IV pJIA-study, which did not use siliconized syringes). It is agreed with the MAH that in this study set up undoubtedly uncertainties on this issue will remain related to silicone issue, however, the issue will not be pursued further. Nonetheless, the findings on immunogenicity in general are considered as valuable information for prescribers, and thus the SmPC should be updated to include

this novel information in the upcoming post article 46 type II variation. In addition, recognising the overall limited information that is available with respect to immunogenicity, the issue of immunogenicity should be further followed by the MAH. Immunogenicity will be re-evaluated at the 5-year follow-up of Study IM101301 as part of a separate post-authorisation commitment by the date specified in the RMP.

Conclusions

Issue resolved.

Question 7

Section 5.1. of the SmPC describes 15 patients in the 2 - 5 year age cohort as ongoing in the 2-year period, and this section should be updated within 60 days of finalisation of the Art. 46 process.

MAH response

The MAH agrees to update Section 5.1 of the SmPC to describe that there are no ongoing patients in the 2 through 5 year age cohort in the 2 year period. The ORENCIA solution for injection in pre-filled syringe SmPC Section 5.1 Pharmacodynamic properties will be modified as follows (see response to Question 5): *Of the 219 subjects treated, 205 completed the short-term period and 200 entered the long-term extension period. In the 2 to 5 year age cohort, 39 (84.8%) patients completed two years. In the 6 to 17 year age cohort, 132 (76.3%) patients completed two years.*

The updated SmPC will be part of the Type II variation to be submitted within 60 days after completion of this Article 46 procedure (EMEA/H/C/000701/P46/064).

Assessment MAH response

The MAH has agreed to update section 5.1 of the SmPC as requested in a type II variation within 60 days after completion of this Article 46 procedure (EMEA/H/C/000701/P46/064).

Conclusions

Issue resolved.

Question 8

The RMP should be updated within 60 days of finalisation of the article 46 process to state that the 2-year results have been submitted.

MAH response

The MAH agrees to submit an updated RMP to reflect that the 2-year results for Study IM101301 have been submitted. The updated RMP will be part of the type II variation to be submitted within 60 days after completion of this Article 46 procedure (EMEA/H/C/000701/P46/064).

Assessment MAH response

The MAH has, as requested, agreed to update the RMP within 60 days of finalisation of the article 46 procedure, to state that the 2-year results have been submitted.

Conclusions

Issue resolved.