

CLINICAL REVIEW

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Reviewer Name	Keith M Hull, MD, PhD
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Established Name	Abatacept
(Proposed) Trade Name	ORENCIA
Therapeutic Class	Fusion Protein
Applicant	Bristol-Myers Squibb
Formulation	Subcutaneous Injection (PFS)
Dosing Regimen	• 10 to < 25 kg: abatacept 50 mg (0.4 mL PFS) • 25 to < 50 kg: abatacept 87.5 mg (0.7 mL PFS) • ≥50 kg: abatacept 125 mg (1 mL PFS)
Indication	Treatment of Juvenile Idiopathic Arthritis
Intended Population(s)	Children with moderate to severe Polyarticular Juvenile Idiopathic Arthritis ages 2-17 years of age

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1 Recommendations/Risk Benefit Assessment

Bristol-Myers Squibb (Applicant) is submitting the current supplemental Biological License Application (sBLA) to support the use of weight-tiered dosing of subcutaneous (SC) abatacept for the treatment of polyarticular Juvenile Idiopathic Arthritis (JIA) in children ages ≥ 2 years of age.

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of the weight-tiered dosing regimen of SC abatacept for the treatment of polyarticular JIA in children ≥ 2 years of age.

1.2 Risk Benefit Assessment

The current submission contains data from Study IM101301 that was used to support the approval of weight-tiered dosing of SC abatacept for the treatment of JIA in children ages ≥ 2 years of age.

Study IM101301 was designed as an open-label study with a 4-month short-term period followed by a long-term extension period that assessed the PK, safety, and efficacy of SC abatacept in 205 children with active JIA ages 2 to 17 years of age. Subjects were enrolled into two cohorts: 2 to 5 years old (n=32 as of August 2015) and 6 to 17 years old (n=173). Subcutaneous abatacept was administered weekly as a weight-tiered dosing regimen that was predicted to provide a systemic exposure comparable to the therapeutic range observed with IV abatacept treatment. Subjects were allowed to continue stable doses of background methotrexate, NSAIDs, and corticosteroids. Abatacept was administered using three different prefilled syringe (PFS) presentations based on subject weight as follows:

- 10 to < 25 kg: abatacept 50 mg (0.4 mL PFS)
- 25 to < 50 kg: abatacept 87.5 mg (0.7 mL PFS)

- ≥ 50 kg: abatacept 125 mg (1 mL PFS)

The study met the prespecified primary endpoint that assessed the abatacept C_{min}ss at Day 113. As a whole, the PK data demonstrated that children with JIA, 2 to 17 years of age, who were administered weekly doses of weight-tiered SC abatacept achieved the desired target therapeutic C_{min}ss of ≥ 10 mcg/mL, thus supporting the approval of SC abatacept for the treatment of JIA. The reader is referred to the Clinical Pharmacology review by Jianmeng Chen, MD, PhD for a detailed analysis of the PK data related to the current submission.

Review of the safety data for up to 24-months following administration of weight-tiered SC abatacept in children with JIA ages 2 to 17 years old did not identify any new safety signals and was consistent with the safety profile seen in the clinical development program and reported in the current package insert.

Overall, the data presented in the current application supports approval of weight-tiered SC abatacept for the treatment of JIA in children ≥ 2 years of age.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are being recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Clinical Postmarketing Requirement

- Applicant to provide long-term safety data in children age 2 to 5 years old treated for ≥ 2 years with SC abatacept to evaluate the risk of malignancies, autoimmune diseases, and serious infections. Patients should be followed a minimum of five years.

2 Introduction and Regulatory Background

The current sBLA is submitted by Bristol-Myers Squibb to support approval of a new dosage form and new route of administration (SC) of abatacept for the treatment of polyarticular JIA in patients 2-years of age and older. The intravenous (IV) form of abatacept is currently approved for the treatment of patients with JIA 6 years of age and older. The primary data in support of this application are derived from a single study, Study IM101301, which is also a Pediatric Research Equity Act (PREA)-required study and that was conducted under a Written Request.

Based on data from animal studies, the Agency has previously waived the requirements for pediatric studies in children with JIA younger than 6 years of age due to theoretical concerns that manipulation of CTLA-4 regulatory pathways in the developing immune system could result in an increased risk of autoimmunity. However, the Applicant submitted pharmacokinetic (PK), safety, immunogenicity, and efficacy data for 32 patients with JIA ages 2 to 5 years old who were treated with SC abatacept. These data were deemed sufficient to allow for the determination of the risk-benefit assessment, and ultimately, approval in this age group.

Background

Juvenile Idiopathic Arthritis is an umbrella term used to encompass several different subtypes of arthritis in pediatric patients defined by the International League of Associations for Rheumatology (ILAR), a classification system currently used by the rheumatology academic community. Broadly speaking, JIA is defined as arthritis of ≥ 1 joint occurring ≥ 6 weeks in a child younger than 16 years of age, and in the absence of other diagnoses (such as infections, malignancy, trauma, reactive arthritis, and specific connective tissue diseases such as systemic lupus erythematosus). Juvenile Idiopathic Arthritis affects an estimated 294,000 children younger than 17 years old in the United States.¹ The incidence, prevalence and disease characteristics of JIA vary worldwide,

reflecting genetic and environmental factors that influence the disease phenotype. Polyarticular JIA represents the subtype that is most similar to adult rheumatoid arthritis, and constituted the diagnosis most common in the majority of subjects enrolled in Study IM101301.

2.1 Product Information

Abatacept is a recombinant, soluble fusion protein consisting of the extracellular domain of human CTLA-4 and the hinge CH2-CH3 regions of the Fc domain of human IgG1, which has been modified to prevent complement fixation and antibody dependent cellular cytotoxicity. CTLA-4 is an endogenous competitive inhibitor of co-stimulation, binding B7-1 and B7-2 ligands with higher affinity than CD28, preventing the co-stimulatory signal. The interaction between CD28 and the B7-1/B7-2 ligands is required to obtain full T cell activation. Abatacept, being a CTLA-4 fusion protein, also binds the ligands B7-1 and B7-2 on antigen presenting cells and thereby inhibits their binding to the T cell co-stimulatory receptor CD28 on T cells. Thus, by antagonizing this interaction, abatacept inhibits T cell activation as well as the activation of other inflammatory effector cells, e.g., macrophages, B cells, and synoviocytes.

2.2 Currently Available Treatments for Proposed Indications

The most relevant biologic treatments currently available for the treatment of polyarticular JIA include etanercept (Enbrel), adalimumab (Humira), tocilizumab (Actemra), etanercept-szzs (Erelzi), adalimumab-atto (Amjevita), and intravenous abatacept (Orencia; children ages ≥ 6 years old).

2.3 Availability of Proposed Active Ingredient in the United States

Abatacept is currently available in the US as a lyophilized powder in preservative-free, single-use vials. Each Orencia vial provides 250 mg of abatacept for IV administration,

1 M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," *Pediatrics in Review*, 2012; 33:303-313

which is to be administered as a 30-minute intravenous infusion. The IV dosage is dependent on patient body weight as follows:

- <60 kg: Orencia 500 mg
- 60 kg-100 kg: Orencia 750 mg
- >100 kg: Orencia 1000 mg

Abatacept is also available in two PFS presentations (125 mg) for weekly SC administration for rheumatoid arthritis patients: a PFS with flange extender; and a PFS with Ultrasafe Passive™ needle guard and flange extenders (the current commercial presentation of the PFS).

Recently, a single-use autoinjector was approved that consisted of a PFS and a device that provides automated needle insertion and delivery of abatacept 125 mg/syringe. The drug product formulation in the prefilled syringe used in the AI presentation is identical to the formulation in the other two PFS presentations currently marketed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Intravenous abatacept was first approved in the U.S. on December 23, 2005 for the treatment of rheumatoid arthritis and approved for JIA patients ages ≥6 years old on April 7, 2008. A SC formulation of abatacept was approved for RA patients on July 29, 2011 with the following post-marketing required (PMR) study to address the requirements of PREA:

PMR#1: Conduct a PK/safety study of SC abatacept in polyarticular JIA patients ages 6 to 17 years of age.

- Final Protocol Submission: November 2012
- Study Completion: September 2017
- Final Report Submission: January 2018

The Agency waived the pediatric study requirement for ages ≤5 years old because there was evidence suggesting that the drug product could be potentially ineffective and

unsafe in this pediatric group. Given that the safety and efficacy of abatacept has not been established in pediatric patients ≤ 6 years of age, abatacept was not recommended for use in this age group.

Given the well-established efficacy and safety profile of IV/SC abatacept in patients with rheumatoid arthritis and IV abatacept in JIA, as well as the consistent exposure-response relationship, the Agency considered that an efficacy study of SC abatacept in pediatric JIA patients was not necessary. Instead, the Agency recommended to Applicant that the pediatric SC study of abatacept in JIA patients could entail a PK study with an open-label safety assessment of sufficient duration to assess adverse events (AEs) with longer latency (i.e. 6-12 months) and efficacy outcome measures as a secondary endpoint to confirm the expected exposure-response relationship.

Subsequently, a Written Request was issued on September 13, 2013 to include study IM101301, a pharmacokinetic and safety study of SC abatacept in patients with JIA ages 6 to 17 years of age. The primary objective of the study is to estimate the abatacept steady state trough concentration (C_{minss}) in children and adolescents ages 6 to 17 years old diagnosed with JIA. Secondary objectives included assessment of efficacy and safety of abatacept administered subcutaneously in JIA patients and assessment of C_{min} as agreed upon with the agency by each weight-tiered dosing category. Weight-tiered dosing is intended to accommodate fixed subcutaneous doses while maintaining systemic exposure within the target therapeutic range defined by the previously performed IV JIA study. Study IM101301 enrolled patients with JIA between ages 2 to 5 years old to address the requirements from other regulatory agencies. The PK, and descriptive safety, efficacy, and immunogenicity data for these patients were also submitted in this supplement for completeness. The Applicant did not formally seek an indication for this age group with this supplement.

To satisfy the conditions of the Written Request, the Applicant has also submitted long-term cumulative safety data from an ongoing registry, supplemented with additional claims-based safety data.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not interfere with reaching conclusions on safety and efficacy.

Each of the studies used to support this application reported protocol violations. A protocol violation was defined as departure from the approved protocol including nonadherence on the part of the patient, the investigator, or the Applicant to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or Good Clinical Practice guidelines, noncompliance to study drug administration, or use of prohibited medications. Overall, the type and small numbers of protocol violations reported in the current application are not expected to compromise the quality of the data or to interfere with the ability to reach conclusions regarding the safety and efficacy of ORENCIA Clickject in adult subjects with RA.

3.2 Compliance with Good Clinical Practices

All clinical studies were conducted in accordance with the clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56 and 312), and International Conference on Harmonization (ICH) Guidelines, that have their origin in the Declaration of Helsinki.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. A total of 225 investigators participated in the clinical study submitted to this application. No principal investigator or subinvestigators had financial

information to disclose to the covered studies. Financial disclosure information for two investigators were not available despite due diligence by the Applicant.

Review of the submitted and signed Forms 3454: "Certification: Financial Interests and Arrangements of Clinical Investigators" does not raise concerns regarding the integrity of the submitted data to the current application.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Control (CMC) review team recommends approval of the sBLA based on the following reasons:

- The drug substance (DS) and bulk drug product (DP) used in the two new fill volumes (0.4-mL and 0.7-mL) are the same as those used in the currently approved 1.0-mL PFS presentation.
- Although two alternate syringe barrels are proposed for all three fill volumes, the contact materials of primary packaging are the same as those for the currently approved PFS product. There is a difference in the amount of (b) (4) in contact with the formulation based on the barrel type and/or fill volume. The levels of residual (b) (4) are controlled through the syringe specification for (b) (4). The sponsor provided sufficient justification and data to support that this difference does not impact product quality.
- There is no difference in the DP manufacturing process between the proposed process for all three fill volumes and the current commercial process for the 1.0-mL PFS presentation, except (b) (4).
(b) (4)
(b) (4). The sponsor performed a process validation study to support manufacturing consistency and the (b) (4) strategy.
- The sponsor provided sufficient stability data demonstrating that the two new fill volumes are stable when stored at long-term storage conditions (2-8 °C) for up to 18 months. In addition, the sponsor showed that the stability data for the two new fill volumes are comparable to that for the

currently approved 1.0-mL PFS presentation, including the primary degradation pathways, at long-term storage condition. Therefore, the approved 24-month shelf life for 1.0-mL PFS presentation is applicable to the two new fill volumes.

- The sponsor provided a comparability protocol to support the implementation of the automated secondary packaging process and a new all (b) (4) carton for all three fill volumes of PFS presentation. The protocol is adequate and acceptable.
- The proposed changes regarding functionality testing of syringe, syringe in-process inspection, and device assembly process are recommended to be approved by CDRH.

The reader is referred to the full CMC review by ZhenZhen Liu, PhD.

4.3 Pharmacology/Toxicology

No new pharmacology/toxicology studies were deemed necessary or were submitted with this supplemental application. The juvenile animal studies supporting dosing in pediatric patients were reviewed in the supplemental BLA for the intravenous abatacept for PJIA in the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP), the review Division then. A brief summary of the results from these studies is as follows:

Three immunotoxicity studies were conducted in juvenile and adult rats. Data demonstrated that abatacept induced more severe adverse effects if administered in juvenile as compared to adult animals. Altered T-cell subsets, including reduced T-regulatory cells and structural changes in spleen and lymph node including decreased size of B-cell areas and increased size of T-cell areas, were observed in juvenile rats. Thyroiditis and pancreatic islet cell inflammation were observed in animals treated with abatacept from juvenile and adult period, attributed to autoimmunity. The incidence and severity appeared to be age and dependent for thyroiditis, but not for the isletitis.

Overall, juvenile rats were found to be more sensitive to abatacept-induced adverse effects. The immunosuppressive effects of abatacept including structural changes in the spleen and lymph nodes as well as altered T-cell subsets were generally more severe in animals with dosing started from juvenile period, regardless of the dosing initiation age, as compared to animals treated during adult period. Abatacept-induced autoimmunity was more severe in animals dosed from PND 4 when the rat immune system is not mature as compared to animals dosed from PND 28 when the rat immune system is largely mature and animals dosed during adult. Therefore, the possibility of abatacept effects on the developing immune system cannot be excluded.

The pharmacology/toxicology team concluded that these data raised concerns supporting the decision to waive the requirements for pediatric studies in patients 6 years old or younger. This was a reasonable precaution in light of the relatively novel mechanism of action of abatacept and the availability of other therapies for JIA. Of note, this assessment had qualified the risk as theoretical. However, the clinical data submitted in this supplement for JIA patients ages 2 to 5 years old, includes safety and immunogenicity data for 6 to 12 months exposure to abatacept. These data are reassuring and sufficient to inform the risk-benefit profile of abatacept in this age group.

4.4 Clinical Pharmacology

Study IM101301 was designed as an open-labeled PK study with the primary endpoint prespecified to assess the abatacept C_{minss} at Day 113. Analysis of the PK data demonstrated that the weekly weight-tiered SC abatacept dosing regimen achieved the desired target therapeutic C_{minss} of ≥ 10 mcg/mL in 130 out of 131 subjects in the 6-17 year-old cohort with a reported geometric mean of 40 mcg/mL. Pharmacokinetic data available from 19 subjects in the 2-5 year-old cohort also demonstrated abatacept C_{minss} ≥ 10 mcg/mL at Day 113 with a geometric mean of 48 mcg/mL, which is comparable in magnitude to the data observed in the 6-17 year-old cohort.

As a whole, the PK data demonstrated that children with JIA, 2 to 17 years of age, who were administered weekly doses of weight-tiered SC abatacept achieved the desired target therapeutic C_{minss} of ≥ 10 mcg/mL, thus supporting the approval of SC abatacept for the treatment of JIA.

The reader is referred to the Clinical Pharmacology review by Jianmeng Chen, MD, PhD for a detailed analysis of the PK data related to the current submission.

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5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1. Studies Used in the Assessment of SC Abatacept for JIA

Study #:	Trial Design	Treatment Arms	Subjects (n)	Efficacy Endpoints
IM101301: Pharmacokinetic Study	MC, OL, R, PG, SD, PK study assessing SC ABA in JIA subjects ages 2-17 years with an inadequate response to non-biologic and/or biologic DMARD	<u>SC ABA based on weight-tier Qwk:</u> • 10 to < 25 kg: ABA 50 mg • 25 to < 50 kg: ABA 87.5 mg • ≥50 kg: ABA 125 mg	ST: • 2-5 y.o. (n=32) • 6-17 y.o. (n=173)	Primary: • Cminss @ Month 4 Secondary: • ACRp30 @ Day113

MC: multicenter; SC: subcutaneous; JIA: Juvenile Idiopathic Arthritis; ABA: abatacept; ST: Short-Term Period; OL: open-label; PK: pharmacokinetic; ACRp: ACR pediatric

5.2 Review Strategy

Study IM101301 was designed as an open-label study with a 4-month short-term period followed by a long-term extension period that assessed the PK, safety, and efficacy of SC abatacept in 205 children with active JIA ages 2 to 17 years of age. Subjects were enrolled into two cohorts: 2 to 5 years old (n=32 as of August 2015) and 6 to 17 years old (n=173). The younger cohort was included by the Applicant to fulfill a requirement from other regulator agencies as well as to expand the clinical experience of abatacept into this age group. This portion of the study is still ongoing in the long-term extension period.

Subcutaneous abatacept was administered weekly as a weight-tiered dosing regimen that was predicted to provide a systemic exposure comparable to the therapeutic range observed with IV abatacept treatment. Subjects were allowed to continue stable doses of background methotrexate, NSAIDs, and corticosteroids. Abatacept was administered using three different PFS presentations based on subject weight as follows:

- 10 to < 25 kg: abatacept 50 mg (0.4 mL PFS)
- 25 to < 50 kg: abatacept 87.5 mg (0.7 mL PFS)

- ≥50 kg: abatacept 125 mg (1 mL PFS)

The primary objective of this open-label study was to estimate the abatacept steady state trough concentration (C_{minss}) in children and adolescents ages 6 to 17 years old who were diagnosed with JIA. Therefore the primary endpoint was a PK parameter and secondary efficacy measures were only descriptive in nature given the open-labeled nature of the study and the lack of a control group. Safety analyses were also limited to descriptive statistics given the lack of a comparator arm. Therefore, the review of safety data was primarily focused on identifying new safety signals with emphasis on autoimmune disorders given the theoretical concerns regarding the manipulation of CTLA-4 regulatory pathways in the developing immune system that could hypothetically result in an increased risk for autoimmunity.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Clinical Studies

5.3.1.1 IM101301

Study IM101301, entitled “*A Phase 3 multicenter, 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 (DMARDs)*”, was an open-label study with a 4-month short-term period followed by a long-term extension period that assessed the pharmacokinetics (PK), safety, and efficacy of SC abatacept in 205 children, ages 2 to 17 years of age, with active juvenile idiopathic arthritis. The study was initiated August 30, 2013 and is currently ongoing with subjects still enrolled in the long-term extension period. A total of 50 study sites conducted the study in the following 12 countries: Argentina, Belgium, Brazil, France, Germany, Italy, Mexico, Peru, Russian Federation, South Africa, Spain, and the United States.

Subjects were enrolled into two cohorts: 2 to 5 years old (n=32 as of August 2015) and 6 to 17 years old (n=173). The younger cohort was included by the Applicant to fulfill a requirement from other regulatory agencies as well as to expand the clinical experience of abatacept into this age group. Enrolled subjects had active polyarticular disease (≥ 3 months) and an inadequate response to at least one nonbiologic or biologic DMARD. The majority of subject subtypes at study entry included Polyarticular disease ($>80\%$) with the remainder classified as Extended and Persistent Oligoarticular, Enthesitis-Related Arthritis, and Systemic disease.

Subcutaneous abatacept was administered weekly as a weight-tiered dosing regimen that was predicted to provide a systemic exposure comparable to the therapeutic range observed with IV abatacept treatment. Subjects were allowed to continue stable doses of background methotrexate, NSAIDs, and corticosteroids. Abatacept was administered using three different PFS presentations based on subject weight as follows:

- 10 to < 25 kg: abatacept 50 mg (0.4 mL PFS)
- 25 to < 50 kg: abatacept 87.5 mg (0.7 mL PFS)
- ≥ 50 kg: abatacept 125 mg (1 mL PFS)

Major Inclusion Criteria:

- Males and females aged 2 to 17 years old with screening weights of ≥ 10 kg
- Informed consent of the subject and/or legal guardian
- Fulfilled ILAR criteria for “polyarticular-course JIA” (polyarticular RF+, polyarticular RF-, PsA, enthesitis-related arthritis, systemic JIA, and extended oligoarticular), with any systemic JIA manifestations absent ≥ 6 months prior to enrollment
- A history of ≥ 5 active joints with active disease, and active articular disease at the time of the study defined as:
 - ≥ 2 active joints (e.g., swelling and/or loss of motion accompanied by pain, tenderness, or both)
 - ≥ 2 joints with LOM at screening and at Day 1
 - The same joint could separately meet the definitions of ‘active joint’ and ‘joint with LOM’
- Insufficient therapeutic response (≥ 3 months) or prior intolerance to ≥ 2 non-biologic DMARD, TNF antagonist or other biological DMARD

Major Exclusion Criteria:

- Subjects with any other rheumatic diseases except for JIA
- Medical history and concurrent diseases including:
 - Active systemic disease ≤ 6 months prior to first dose of study drug
 - Macrophage activation syndrome ≤ 6 months prior to first dose of study drug
 - Active uveitis ≤ 6 months of enrollment
 - Subjects with persistent oligoarthritis JIA
 - Subjects who received treatment abatacept
 - Subjects who have failed responses to ≥ 2 TNF antagonists or other biologic DMARD
 - Presence of an active infection, serious infections or history of frequent infection or chronic infections ≤ 3 months prior to the first dose of drug
 - Received live vaccines within 3 months of enrollment
 - Active vasculitis of a major organ system
 - Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, neurological, or cerebral disease
 - Presence at screening or history of any disease other than JIA that requires the use of chronic systemic corticosteroids
 - History of cancer within ≤ 5 years
 - History of opportunistic infections
 - Evidence of active or latent bacterial, viral or fungal infections
 - Subjects at risk for TB
- Physical and laboratory test findings including:
 - HBV antigen
 - HCV antibody
 - Hemoglobin ≤ 9.0 g/dL
 - WBC $\leq 2 \times 10^9/L$
 - Platelets $\leq 150 \times 10^9/L$
 - Serum creatinine ≥ 1.5 times ULN
 - Serum ALT or AST ≥ 2 times ULN

The primary efficacy endpoint was the estimated abatacept steady-state trough concentration (C_{minss}) at Day 113 in children with JIA ages 2 to 17 years of age.

Major secondary endpoints included assessment of the safety of SC abatacept in the JIA subjects as well as efficacy parameters as measured by the ACR pediatric 30 on Day 113. The ACR pediatric 30 (ACRp30) was defined as $\geq 30\%$ improvement in ≥ 3 of the 6 JIA core set variables:

- Number of active joints
- Physician global assessment of disease activity
- Parent global assessment of patient overall well-being
- Functional ability as measured by the CHAQ
- Laboratory measure of inflammation as measured by the CRP and ≥ 305 worsening in not more than 1 of the remaining JIA core set variables

Additional secondary endpoints included the proportion of subjects achieving ACRp50, ACRp70, ACRp90, and ACRp100. Descriptive statistics were used for efficacy analyses.

Safety assessments were based on medical review of AE reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated and reviewed for potential significance and clinical importance. The immunogenicity of abatacept following SC administration in this patient population was also assessed. Descriptive statistics were used for safety analyses.

There were a total of 13 amendments made to the protocol. Ten of the amendments were site specific and three that affected all study sites. Site-specific protocol amendments included: restricting the age of study participants to ≥ 6 years old (USA, Peru, Argentina, and Brazil), changes regarding HIV screening (Argentina, Peru, France, and South Africa), extension of the long-term extension period up to 5-years in subjects who demonstrated clinical benefit (Germany, France, Italy, and Belgium), and changes to comply with local laws regarding access to post-study therapy (Brazil). Generalized protocol amendments included addition of a pneumococcal vaccine substudy in subjects 2-5 years of age (where permissible) that was subsequently amended to a DTP vaccine substudy, elimination of CHQ and JAMAR Questionnaires, clarification of seven days post-dose follow-up visits, and amendment of inclusion/exclusion criteria to allow subjects with PsA or enthesitis-related arthritis and

revision of pregnancy testing requirements. Overall, the protocol amendments did not change the interpretability of the study or negatively impact the safety of the subjects enrolled in the study.

Overall, the protocol amendments did not change the interpretability of the study or negatively impact the safety of the subjects enrolled in the study.

Subject Disposition: 6 to 17 year-old subject cohort

A total of 173 subjects were enrolled into 6 to 17 year-old cohort for the short-term period of the study. A total of nine (5%) subjects discontinued the study during this period due to AEs (n=3; 2%), lack of efficacy (n=3; 2%), withdrawal of consent (n=2; 1%), or poor compliance (n=1; 1%). At the end of the short-term period 157 out of 173 (91%) eligible subjects entered the long-term extension period. An additional eight subjects discontinued during the long-term extension period due to AE (n=1), lack of efficacy (n=6), and subject no longer met study criteria (n=1). All randomized subjects were included in the Safety and Intent-to-Treat populations and no data were excluded.

Subject Disposition: 2 to 5 year-old subject cohort

A total of 32 subjects were enrolled into 2 to 5 year-old cohort for the short-term period of the study. Of these, 27 (84%) subjects remained in the study at the time of database closure in the short-term or long-term extension period. The interim data at the time of the Applicant's submission reported a total of five (15%) subjects discontinuing due to lack of efficacy during either the short-term (n=2) or long-term extension (n=2) periods of the study. One subject discontinued due to an inability to attend monthly office visits. All randomized subjects were included in the Safety and Intent-to-Treat populations and no data were excluded.

Protocol deviations during all phases of Study IM101301 were reported in 38 (22%) subjects with the most common protocol deviations reported as follows:

- Inclusion/exclusion deviations: n=15

- Failure to obtain written informed consent: n=6
- Use of prohibited concomitant medications: n=4
- Incorrect dosing or study treatment assignment: n=2

These protocol deviations are not expected to impact the analysis and interpretation of the results for Study IM101301.

Overall, the baseline demographics reflected the US JIA population of children with the majority of enrolled subjects being white (85%) and female (76%). Subjects in the 6 to 17 year-old cohort had a mean duration of JIA of 2.8 years (59% of subject were diagnosed < 2-years), an average of 12 active joints, 11 joints with limitation of motion, and a mean CHAQ disability score of 0.99. Not surprisingly, subjects in the 2-5 year-old cohort had a shorter duration of disease (0.7 years) but demonstrated similar severity with an average of 9 active joints, 8 joints with limitation of motion, and a mean CHAQ disability score of 1.05.

Both cohorts of subjects reported a similar history of concomitant medications that included NSAIDS (~75%), methotrexate (~80%), and corticosteroids (~35%). Only two subjects from the 6-17 year-old cohort and three subjects from the 2-5 year-old cohort reported previous use of a biologic drug.

6 Review of Efficacy

As discussed in Section 5, Study IM101301 was designed as an open-labeled PK study with the primary endpoint prespecified to assess the abatacept C_{minss} at Day 113. Analysis of the PK data demonstrated that the weekly weight-tiered SC abatacept dosing regimen achieved the desired target therapeutic C_{minss} of ≥ 10 mcg/mL in 130 out 131 subjects in the 6-17 year-old cohort with a reported geometric mean of 40

mcg/mL Pharmacokinetic data available from 19 subjects in the 2-5 year-old cohort also demonstrated abatacept C_{minss} ≥10 mcg/mL at Day 113 with a geometric mean of 48 mcg/mL, which is comparable in magnitude to the data observed in the 6-17 year-old cohort.

As a whole, the PK data demonstrated that children with JIA, 2 to 17 years of age, who were administered weekly doses of weight-tiered SC abatacept achieved the desired target therapeutic C_{minss} of ≥10 mcg/mL, thus supporting the approval of SC abatacept for the treatment of JIA. The reader is referred to the Clinical Pharmacology review by Jianmeng Chen, MD, PhD for a detailed analysis of the PK data related to the current submission.

The Applicant also submitted data for secondary efficacy endpoints assessing ACRp responses in subjects over time. A brief summary of these endpoints will be included in this review despite the fact they that the study was open-label and without a control group,

ACRp responses during the short-term period: 6 to 17 year-old cohort

As shown in Table 1, 140 out of 173 (81%) subjects achieved an ACRp30 response at Day 113. A clinical response was first observed at Day 29 and appeared to plateau by Day 85.

Table 2. Proportion of Subjects Achieveing ACRp30 Over Time

Study Day	Weight-Tiered Abatacept SC (N=173)
Day 29 n (%) 95% CI	103 (60) (52, 67)
Day 57 n (%) 95% CI	127 (73) (67, 80)
Day 85 n (%)	140 (81) (75, 87)

95% CI	
Day 113 n (%) 95% CI	140 (81) (75, 87)
Source: Clinical Study Report for Study IM101301 6-17 year-old Cohort, Table 7.2.3.1-1, Page 65	

ACRp 50, 70, 90, and 100 responses were also observed at Day 113 (Table 3).

Table 3. Proportion of Subjects Achieving ACRp50, 70, 90, 100 at Day 113

Study Day	Weight-Tiered Abatacept SC (N=173)
ACRp50 n (%) 95% CI	123 (71) (64, 78)
ACRp70 n (%) 95% CI	91 (53) (45, 60)
ACRp90 n (%) 95% CI	50 (29) (22, 36)
ACRp100 n (%) 95% CI	25 (15) (9, 20)
Source: Clinical Study Report for Study IM101301 6-17 year-old Cohort, Table 7.2.3.2-1, Page 68	

Subgroup analyses were performed using the proportion of subjects achieving an ACRp30 at Day 113 based on weight-tier dosing regimen, JIA subtype, DMARD/biologic use, baseline demographics, and disease activity. In general, all subgroup analyses demonstrated clinical benefits consistent with the results observed in the broader ACRp30 assessments.

ACRp responses during the short-term period: 2 to 5 year-old cohort

Similar proportions of subjects in the 2-5 year-old cohort achieved ACRp 30, 50, 70, 90, and 100 responses at Day 113 compared to subjects in the 6-17 year-old cohort (Table 4).

Table 4. Proportion of Subjects Achieving ACRp30, 50, 70, 90, and 100 at Day 113

Study Day	Weight-Tiered Abatacept SC (N=30)
ACRp30 n (%) 95% CI	26 (87) (75, 99)
ACRp50 n (%) 95% CI	25 (83) (70, 97)
ACRp70 n (%) 95% CI	21 (70) (54, 86)
ACRp90 n (%) 95% CI	15 (50) (32, 68)
ACRp100 n (%) 95% CI	10 (33) (17, 50)

Source: Clinical Study Report for Study IM101301 2-5 year-old Cohort, Table S.5.4, Page 88

No subgroup analyses were performed for the 2 to 5 year-old cohort due to the small number of subjects.

Despite the limitations of the clinical efficacy data, the overall results are supportive for the approval for treatment of JIA in children ages 2 to 17 years old using the proposed weight-tiered based dosing regimen of SC abatacept.

7 Review of Safety

The safety of abatacept for use in the treatment of rheumatoid arthritis and JIA has been well characterized in numerous well-conducted clinical studies using both the IV and SC formulations. Safety analyses for the present study were limited due to the lack of a comparator arm. Therefore, the review of safety data was primarily focused on identifying new safety signals with emphasis on autoimmune disorders given the theoretical concerns regarding the manipulation of CTLA-4 regulatory pathways in the developing immune system that could hypothetically result in an increased risk for autoimmunity.

Overall, the safety profile following administration of weight-tiered SC abatacept in children with JIA ages 2 to 17 years old did not identify any new safety signals and was consistent with the safety profile seen in the clinical development program and reported in the current package insert.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As described in Section 5, Study IM101301 was an open-label PK study conducted in subjects ages 2 to 17 years old with JIA to assess the PK of abatacept following weekly weight-tiered SC abatacept dosing. The study was divided into a 4-month short-term period to assess PK parameters and subsequently followed by a 20-month long-term extension period. Given that this study was open-labeled and without a control arm, the review of the safety data entails analysis of the full 24-month cumulative period (short-term and long-term extension periods) rather than the individual treatment periods. The individual subject cohorts will be discussed separately.

7.1.2 Categorization of Adverse Events

All safety evaluations were conducted and reported according to Good Clinical Practice guidelines with data collected for AEs, clinical laboratory test results, and vital signs. Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries and pre-defined lists of preferred terms (PTs) were developed by the Applicant and used to analyze the data for safety events.

Adverse events were included in the safety analysis if the onset date was on or after the first dose start date of a specified period. Subject listings included all AEs.

All AEs were coded and grouped into PTs by system organ class (SOC), using the most current version of the MedDRA. Unless specified otherwise, listings and summaries were based on SOCs and PTs using the primary path.

7.3 Major Safety Results

7.3.1 Deaths

6-17 year-old subject cohort

No deaths were reported in this subject cohort during Study IM101301.

2-5 year-old subject cohort

No deaths were reported in this subject cohort during Study IM101301.

7.3.2 Nonfatal Serious Adverse Events

6-17 year-old subject cohort

A total of 8/173 (5%) subjects experienced ten SAEs during the course of the study and included one case each of pyelonephritis, sepsis, anemia, abdominal pain, chest pain, radius fracture, hypomagnesemia, synovitis, ovarian germ cell teratoma (Stage III), and nephrolithiasis. Only the case of nephrolithiasis was classified as severe in intensity.

2-5 year-old subject cohort

No SAEs were reported in this subject cohort during Study IM101301.

7.3.3 Dropouts and/or Discontinuations

6-17 year-old subject cohort

A total of 4/173 (2%) subjects discontinued due to AEs including fatigue, sepsis, ovarian germ cell teratoma (Stage III), and exanthemous rash. Review of the safety narratives suggest that the reports of fatigue, sepsis, and exanthemous rash may have been related to study drug. However, these types of AEs are consistent with the known adverse reaction profile of abatacept, and overall, no new safety signals were identified.

2-5 year-old subject cohort

No subject discontinued due to AE in this subject cohort during Study IM101301.

7.3.4 Significant Adverse Events and Adverse Events of Special Interest

7.3.4.1 Infections

6-17 year-old subject cohort

A total of 90/173 (52%) subjects reported an infection during the course of the study. The most common infections were nasopharyngitis (n=34, 20%) and upper respiratory tract infection (n=22, 13%) with other infections occurring in <5% of subjects. Most subjects only experienced a single case of nasopharyngitis (n=24, 71%) and upper respiratory tract infections (n=14, 64%). No infection, except for a single case of sepsis, was reported as severe in intensity. Opportunistic infections were reported by two subjects with one case each of herpes zoster and an oral candida infection. No new safety signals were identified.

2-5 year-old subject cohort

Infections were reported in 22/32 (69%) subjects with the most common infection reported being nasopharyngitis (n=7, 22%), upper respiratory tract infection (n=6, 19%),

conjunctivitis (n=4, 13%), and gastroenteritis (n=4, 13%). Most subjects only experienced a single occurrence of an infectious AE. No opportunistic infections were reported.

7.3.4.2 Autoimmune Disorders

6-17 year-old subject cohort

Autoimmune disorders were reported in 3/173 (2%) subjects from the 6 to 17 year-old subject cohort and included episcleritis, Raynaud's phenomenon, and psoriasis. All of these conditions can be seen in the clinical spectrum of JIA and there did not appear to be a clear relationship to abatacept. No new safety signals were identified.

2-5 year-old subject cohort

No autoimmune disorders were reported in this subject cohort during Study IM101301.

7.3.4.3 Malignancy

6-17 year-old subject cohort

A single case of Stage III ovarian germ cell teratoma was diagnosed on Study Day 99. Review of the safety narrative does not suggest a causal relationship to abatacept.

2-5 year-old subject cohort

No malignancies were reported in this subject cohort during Study IM101301.

7.4.3.4 Local Injection-Site Reactions

6-17 year-old subject cohort

A total of 10/173 (6%) subjects experienced local injection-site reactions with <3% of subjects reporting individual events. The rate and type of local injection-site reaction are consistent with the known adverse reaction profile of abatacept, and overall, no new safety signals were identified.

2-5 year-old subject cohort

No injection-site reactions were reported during the study; however, one subject was reported to have an AE of mild intensity due to “pain at the site of application of study drug”.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

6-17 year-old subject cohort

Adverse events were reported in 127/173 (73%) subjects. The most frequently reported AEs reported during the study in $\geq 3\%$ of subjects included nasopharyngitis (n=34, 20%), upper respiratory tract infection (n=22, 13%), headache (n=15, 9%), pyrexia (n=15, 9%), vomiting (n=11, 6%), urinary tract infection (n=8, 5%), cough (n=7, 4%), influenza (n=7, 4%), abdominal pain (n=6, 4%), gastroenteritis (n=6, 4%), abdominal pain (n=5, 3%), conjunctivitis (n=5, 3%), joint injury (n=5, 3%), pharyngitis (n=5, 3%), and rhinitis (n=5, 3%). Severe intensity of AEs were reported in eight subjects and included five subjects with SAEs (sepsis, nephrolithiasis, anemia, ovarian germ cell teratoma, and chest pain) and three subjects with severe AEs (headache, traumatic hematoma, and hypochromic anemia). All other AE were reported as mild to moderate in intensity.

Analyses of AEs by weight-tier showed similar proportions of AEs in each dosing group that did not scale with dose.

The rate and type of AEs reported in Study IM101301 are consistent with the pediatric population, the clinical spectrum of JIA-related disease, and the known adverse reaction profile of abatacept. Overall, no new safety signals were identified.

2-5 year-old subject cohort

Adverse events were reported in 26/32 (81%) subjects of the 2-5 year-old cohort. The most frequently reported ($\geq 10\%$ of subjects) AEs included nasopharyngitis (7/32; 22%),

pyrexia (7/32; 22%), upper respiratory tract infection (6/32; 19%), conjunctivitis (4/32; 13%), and gastroenteritis (4/32; 13%).

Overall, the type of AEs reported in the 2-5 year-old subject cohort were consistent with the known adverse reaction profile of abatacept.

7.4.2 Laboratory Findings

6-17 year-old subject cohort

Laboratory abnormalities were infrequent and did not tend to persist with continued abatacept dosing. The most common laboratory abnormalities included WBC in urine (37/93; 40%), RBC in urine (25/86; 29%), blood in urine (31/171; 18%), low serum glucose (23/172; 13%), leukocytosis (17/171; 10%), and eosinophilia (11/172; 6%). Persistent laboratory abnormalities, defined as ≥ 2 consecutive days, were observed for WBC, RBC, or blood in urine in 8/93 subjects, 8/86 subjects, and 9/171 subjects, respectively. Subjects reporting RBCs or blood in urine were nearly all female (91%) and over the age of 12 years old (90%) suggesting the findings may be related to menses. Similarly, the majority of subjects with WBCs in urine were female (89%) and over the age of 12 years old (62%). The laboratory abnormalities were observed in subjects who experienced SAEs, autoimmune disorders, or the case of ovarian germ cell teratoma. Of the three subjects reporting autoimmune disorders, one subject had persistent laboratory abnormality in urinary WBCs for two consecutive days.

Nine subjects had clinical laboratory results classified as AEs, but not marked abnormalities, including: proteinuria, elevated liver enzymes, increased GGT, increased ALT, increased blood creatinine, increased weight, decreased weight, and abnormal liver function tests.

2-5 year-old subject cohort

Marked abnormalities in laboratory values were infrequent and typically not persistent. The most common laboratory abnormalities included WBCs in urine (5/16; 31%), low

serum glucose (4/32; 13%), leukocytosis (3/32; 9%), hyperkalemia (3/32; 9%), eosinophilia (2/32; 6%), and elevated creatinine (2/32; 6%). Except for two subjects (elevated alkaline phosphatase, WBCs in urine), no laboratory abnormalities persisted for ≥ 2 consecutive laboratory test days.

7.4.3 Vital Signs

6-17 year-old subject cohort

Mean and median vital signs remained within normal ranges throughout the reported study period in the 6 to 17 year-old subject cohort.

2-5 year-old subject cohort

Mean and median vital signs remained within normal ranges throughout the reported study period in the 2 to 5 year-old subject cohort.

7.6 Additional Safety Evaluations

7.6.1 Immunogenicity

6-17 year-old subject cohort

A total of 4/171 (2%) of subjects tested positive for anti-drug antibodies (ADA) to abatacept relative to baseline in the cumulative period to date. Titers for all positive results were reported as ≤ 40 . Two of the subjects had persistent ADAs, defined as ≥ 2 consecutive positive test results relative to baseline with the same ADA reactivity, for no more than 3 consecutive test visits. No direct correlation between ADA positivity and AEs could be discerned from the data.

2-5 year-old subject cohort

To date, a total of 3/31 (10%) subjects tested positive for ADAs to abatacept relative to baseline. No subject had positive immunogenicity on consecutive scheduled laboratory test days. No direct correlation between ADA positivity and AEs could be discerned

from the data; however, one ADA-positive subject had variable Cmin abatacept concentrations and their ACRp30 and ACRp50 responses fluctuated during the study and was not correlated with positive immunogenicity. The subject never achieved a response greater than ACRp30 and discontinued from the study on Day 310 due to lack of efficacy.

7.6.2 90-day Safety Update

6-17 year-old subject cohort

At the time of the 90-day safety update, three (2%) subjects were still ongoing in the study. A total of 124/173 (72%) subjects have completed the cumulative period. An additional 24 subjects discontinued the studied since the original submission, thus bringing the total to 41/173 (24%) subjects. Reasons for discontinuation among the 24 subjects included AEs (n=3), lack of efficacy (n=8), withdrawal of consent (n=2), subject no longer met study criteria (n=1), pregnancy (n=1), subject request to discontinue study treatment (n=4), and “other” (n=5).

No deaths were reported in the 90-day safety update. Six additional SAEs were reported and included renal calculi, pneumonia, appendicitis, autonomic nervous system imbalance (post-long-term extension), concussion, and vertigo. An additional 23 subjects reported an AE during the interim period all of which were reported as mild to moderate in severity except for one case of severe synovitis. No new cases of malignancy or autoimmune disorders were reported. Overall, the type and severity of infections reported were similar to that observed previously. Injection-site reactions were reported for three additional subjects with mild symptoms injection-site pain and erythema. A single case of renal failure was reported after the database lock for the safety update. Onset of the renal failure occurred 56-days post last study drug dose and resolved within 26 days of onset.

Overall, the types of events reported in the 90-day safety update were similar to those reported in the original submission. No new safety signals were identified.

2-5 year-old subject cohort

A total of 21/46 (46%) subjects have completed the cumulative period of the study. Of the additional seven (15%) subjects who discontinued during the cumulative period, one subject discontinued due to an AE (pyrexia), five subjects discontinued due to lack of efficacy, and one subject discontinued due to a request to discontinue treatment.

No deaths were reported in the safety update. Two subjects experienced an SAE: one case of a febrile seizure (subject noted to have a history of epilepsy) and one case of a subject administered a higher dose of abatacept than recommended due to a recording error but without adverse effects. There were no deaths, malignancies, or autoimmune disorders reported in the 2 to 5 year-old cohort.

In summary, no new safety signals were identified in the interim safety data for subject in the 2 to 5 year-old cohort.

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8 Postmarketing Experience

This is the initial sBLA for SC abatacept in children ages 2 to 17 years old with JIA, therefore, no postmarketing data is available for the current product being reviewed.

9 Appendices

9.2 Labeling Recommendations

The proposed changes include:

- Extension of the JIA indication to include patients from 2 to 5 years of age as well as 6 years of age and older
- Dosing regimen for the SC route of administration for JIA patients
- Clinical data in JIA patients for Section 6 Adverse Reactions, Section 12.3 Pharmacokinetics, and Section 14 Clinical Studies. The review team deleted a proposed presentation of (b) (4)

9.3 Advisory Committee Meeting

Following the initial review and discussion of the application, the review team determined abatacept to be efficacious in children with JIA and with an acceptable safety profile and no identifiable serious safety signals or outstanding issues. Consequently, a determination was made deciding that a meeting of the FDA's Arthritis Advisory Committee would not be required.

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/s/

KEITH M HULL
03/08/2017