CDER Clinical, CDTL, and Division Summary Memo

Date	July 26, 2022
From	Eric J. Gapud, MD PhD
Subject	Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA # and Supplement#	761024/S-010, 761024/S-(b) (4)
Applicant	Amgen, Inc.
Date of Submission	September 29, 2021 (S-010) March 29, 2022 (S-(b) (4))
BSUFA Goal Date	July 29, 2022 (S-010) September 29, 2022 (S-(b) (4))
Proprietary Name	Amjevita (adalimumab-atto)
Reference Product Proprietary Name	Humira
Dosage Form(s)	No new proposed dosage forms
Applicant Proposed Indication(s)/Population(s)	Expansion of existing indications to include the following: • Treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 years to less than 4 years of age • Treatment of moderately to severely active Crohn's disease (CD) in pediatric patients ages 6 years to 17 years of age
Applicant Proposed Dosing Regimen(s)	Proposed dosing regimen is consistent with the reference product dosing regimen. Polyarticular Juvenile Idiopathic Arthritis (2 years of age and older):

Pediatric Weight 2 Years of Age and Older	Recommended Dosage
15 kg (33 lbs) to less than 30 kg (66 lbs)	20 mg every other week
30 kg (66 lbs) and greater	40 mg every other week

<table>
<tr><td></td><td>Pediatric Crohn's Disease (6 years of age and older):
<table>
<tr><th rowspan="2">Pediatric Weight</th><th colspan="2">Recommended Dosage</th></tr>
<tr><th>Days 1 and 15</th><th>Starting on Day 29</th></tr>
<tr><td>17 kg (37 lbs) to less than 40 kg (88 lbs)</td><td>Day 1: 80 mg
Day 15: 40 mg</td><td>20 mg every other week</td></tr>
<tr><td>40 kg (88 lbs) and greater</td><td>Day 1: 160 mg (single-dose or split over two consecutive days)
Day 15: 80 mg</td><td>40 mg every other week</td></tr>
</table></td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Approval</td></tr>
<tr><td>Recommended Indication(s)/Population(s)</td><td>• Moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.
• Moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

(Expansion of existing indications to include pediatric patients with pJIA 2 years to less than 4 years of age and pediatric patients with CD 6 years to 17 years of age)</td></tr>
<tr><td>Recommended Dosing Regimen(s)</td><td>Same as reference product dosing regimen</td></tr>
</table>

1. Introduction

The Applicant submitted supplement 10 to Biologic License Application (BLA) 761024 to expand the indications of polyarticular Juvenile Idiopathic Arthritis (pJIA) to include pediatric patients 2 years to less than 4 years and Crohn's Disease (CD) to include pediatric patients 6 years to 17 years, which were previously under orphan exclusivity. Supplement 10 was submitted to fulfill Pediatric Research Equity Act (PREA) Post-Marketing Requirements (PMRs) 3125-1, 3125-2, and 3125-4 that were issued with the original approval of adalimumab-atto on September 23, 2016. No new clinical information is included nor required for this submission. The Applicant has provided a scientific justification for extrapolation for each of the populations currently being sought for licensure. (b) (4)

(b) (4)

(b) (4)

Supplements 10 and (b) (4) are reviewed below.

2. Background

Adalimumab-atto (Amjevita) is a recombinant human immunoglobulin (Ig) G1 monoclonal antibody (mAb) against tumor necrosis factor (TNF)-alpha. Adalimumab-atto was approved as a biosimilar to US-licensed Humira (US-Humira) on September 23, 2016 under section 351(k) of the Public Health Service Act (BLA 761024), for the treatment of:

1. Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

2. Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.

3. Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with PsA.

4. Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.

5. Adult Crohn's Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab products.

6. Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine. The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF

blockers.

7. Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

The original application included the following:

- A comprehensive comparative analytical assessment of adalimumab-atto, US-Humira, and EU-approved Humira (EU-Humira). This assessment included a comparative characterization of physicochemical attributes and comparative functional assessments.
- Nonclinical studies including 2 one-month, repeat-dose general toxicology and toxicokinetic studies in cynomolgus monkeys to compare the effects of adalimumab-atto to those of US-Humira.
- A pharmacokinetic (PK) similarity study (20110217) in healthy adult subjects following a single SC 40 mg dose of adalimumab-atto, EU-Humira, or US-Humira.
- A comparative clinical study (20210262) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-atto and US-Humira in combination with methotrexate in patients with moderately to severely active RA.
- A second comparative clinical study (20210263) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-atto and EU-Humira in patients with moderate to severe Ps, and safety and immunogenicity in patients undergoing a single transition from EU-Humira to adalimumab-atto.
- A scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) for extrapolation of data and information submitted in the application to support licensure of adalimumab-atto for each of the additional indications for which Amgen, Inc. was seeking licensure and for which US-Humira had been previously licensed.

In considering the totality of the evidence for the original BLA submission, review of the data submitted by the Applicant showed that adalimumab-atto is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between adalimumab-atto and US-Humira in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of adalimumab-atto for the non-studied indications sought for approval. Review of the information submitted by the Applicant demonstrated that adalimumab-atto is biosimilar to US-Humira for each of the following indications for which US-Humira has been previously approved and the Applicant was seeking licensure for adalimumab-atto: RA, pJIA in patients 4 years of age and older, PsA, AS, Ps, adult CD, and adult UC. Refer to the Division Summary (dated September 23, 2016) and Cross-Discipline Team Leader (dated September 22, 2016) reviews for additional details.

Amjevita is approved in the following presentations:

- 40 mg/0.8 mL single-dose prefilled pen

- 40 mg/0.8 mL single-dose prefilled syringe
- 20 mg/0.4 mL single-dose prefilled syringe

At the time of the BLA approval, the following PMRs were required:

- **3125-1**: Assessment of Amjevita (adalimumab-atto) for the treatment of polyarticular JIA in patients ages 2 to less than 4 years of age
  - Final Report Submission September 2021
- **3125-2**: Assessment of Amjevita (adalimumab-atto) for the treatment of pediatric Crohn's disease in patients 6 years to 17 years of age
  - Final Report Submission September 2021
- **3125-3**: Assessment of Amjevita (adalimumab-atto) for the treatment of pediatric UC in patients 5 years to 17 years of age
  - Final Report Submission December 2020
- **3125-4**: Develop a presentation that can be used to accurately administer Amjevita o to pediatric patients who weigh less than 15 kg
  - Final Report Submission September 2021

The Applicant submitted supplemental BLA (sBLA) 10 on September 29, 2021 to provide pediatric assessments to address PMRs 3125-1 and 3125-2 and to update labeling based on these assessments to expand the indications for pJIA to include patients 2 years of age and older, and the indication for CD to include adult and pediatric patients 6 years of age and older. The inclusion of these indications was not sought in the original BLA because of orphan drug exclusivities that have since expired for pJIA and CD. The submission for supplement 10 includes a cross-reference to the scientific justification for extrapolation submitted with the original BLA to support extrapolation for the populations currently being sought for licensure and labeling updates to include the expanded indications and for alignment with the reference product. No new clinical information was included nor required for this submission.

(b) (4)

3. CMC/Product Quality

Supplement 10

For supplement 10, no new product quality information was submitted nor required. There are no CMC or product quality issues that would preclude approval of the indications sought for licensure.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for supplements 10 and (4). There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indications sought for licensure.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for supplements 10 and (b) (4) There are no clinical pharmacology issues that would preclude approval of the indications sought for licensure.

6. Clinical/Statistical-Efficacy

Adalimumab-atto was previously studied in comparative clinical studies in patients with RA (20120262) and Ps (20120263). The data were previously reviewed and summarized in the clinical and statistical reviews, dated September 7, 2016 and September 15, 2016, for the original application. No new clinical/statistical efficacy information was submitted nor required for supplements 10 or (b) (4) There are no clinical/statistical efficacy issues that would preclude approval of the indications sought for licensure.

7. Safety

Adalimumab-atto was previously studied in comparative clinical studies in patients with RA (20120262) and Ps (20120263), and in healthy subjects in a PK similarity study (20110217). The data were previously reviewed and summarized in the clinical review dated September 7, 2016 for the original application. No new safety data were submitted nor required for supplements 10 and (b) (4) There are no clinical safety issues that would preclude approval of the indications sought for approval.

8. Considerations for Extrapolation of Biosimilarity in Other Conditions of Use

The Guidance for Industry Questions and Answers on Biosimilar Development and the Biologics Price Competition and Innovation (BPCI) Act (September 2021) notes that in the context of the potential biosimilar product under the Act, the biosimilar applicant may fulfill the PREA requirements by satisfying the statutory requirements for demonstrating biosimilarity and providing an adequate scientific justification under the BPCI Act for extrapolating data and information to support a licensure for each condition of use for which licensure is sought.[1]

Adalimumab-atto is an approved biosimilar for the treatment of RA, PsA, AS, adult CD, UC, pJIA in patients 4 years of age and older, and Ps. In the original BLA submission, the Applicant provided data and support for biosimilarity, including extensive analytical characterization that demonstrated that adalimumab-atto is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, as well as clinical data that demonstrated that there were no clinically meaningful differences between adalimumab-atto and US-Humira in terms of safety, purity, and potency based on similar clinical PK in healthy subjects and similar efficacy, safety, and immunogenicity in RA and Ps.

Additional points considered in the justification for extrapolation of data and information to support licensure of adalimumab-atto as a biosimilar for each non-studied indication for which licensure was sought and for which US-Humira was previously approved included:

- PK similarity was demonstrated between adalimumab-atto and US-Humira. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-atto and US-Humira in the indications sought for licensure. A similar PK profile would be expected between adalimumab-atto and US-Humira in patients with JIA, PsA, AS, adult CD, and UC.

[1] For more information on extrapolation in this context, see FDA's Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)

- In general, immunogenicity of US-Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications, rather than by patient population, and the results were influenced by the type of assay used[2]. Similar immunogenicity was observed between adalimumab-atto and US-Humira in patients with RA; adalimumab-atto and EU-Humira in patients with Ps; and adalimumab-atto, US-Humira, and EU-Humira in healthy subjects. Therefore, similar immunogenicity would be expected between adalimumab-atto and US-Humira in patients with JIA, PsA, AS, adult CD, and UC.
- There were no clinically meaningful differences between adalimumab-atto and US-Humira in patients with RA nor in healthy subjects. There were also no meaningful differences between adalimumab-atto and EU-Humira in patients with Ps. Coupled with the demonstration of analytical and PK similarity between adalimumab-atto, US-Humira, and EU-Humira, a similar safety profile would be expected in patients with JIA, PsA, AS, adult CD, and UC.
- The Applicant addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that adalimumab-atto and US-Humira have the same mechanisms for each of the sought indications, to the extent that the mechanisms of action are known or can reasonably be determined.

The scientific justification for extrapolation in pJIA submitted with the original BLA included the entire pJIA population for which US-Humira is approved. However, at that time, the Applicant sought licensure for pJIA 4 years of age and older as there was remaining Orphan Drug exclusivity for pJIA 2 years to less than 4 years of age.

In supplement 10, the Applicant has cross-referenced the previously submitted justification for extrapolation of the data and information in support of licensure of adalimumab-atto for the treatment of pJIA in patients 2 years to less than 4 years of age and pediatric CD in patients 6 years to 17 years of age. The justification for extrapolation to support licensure in pJIA 2 years to less than 4 years of age is described below. Refer to Section 16 Appendix: Division of Gastroenterology Memo for discussion of the justification for extrapolation to support licensure in CD 6 years of age and older.

Scientific considerations outlined above for the extrapolation of biosimilarity to the populations of pJIA 4 years of age and older are also relevant for the population of pJIA 2 to less than 4 years of age.

- There is no data or scientific evidence that PK and immunogenicity differ in patients with pJIA 2 years to less than 4 years of age and patients with pJIA 4 years of age and older such that the same justification for extrapolation for extrapolation could not apply.
- In terms of safety and toxicity, the same safety data which supported approval of the non-studied indications in the original application, including pJIA in patients 4

[2] US-Humira prescribing information

years of age and older, are relevant to support safety in patients with pJIA 2 years to less than 4 years of age.

- Regarding the mechanism of action, the shared importance of TNF in the pathophysiology of disease and clinical response in RA and pJIA support extrapolation to the existing pJIA data for the reference product. There are no scientific data that suggest that the mechanism of action differs in patients with pJIA in the 2 years to less than 4 years of age population such that the same justification for extrapolation could not apply to the younger subgroup of pJIA patients.

Therefore, given that there are no data or scientific evidence that the mechanism of action, exposure relationship, immunogenicity, safety, or toxicity of adalimumab-atto are expected to differ between pJIA in patients 2 years to less than 4 years of age and in patients 4 years of age and older, it is reasonable to extrapolate the data and information to support licensure of an expanded indication of adalimumab-atto to include the treatment of patients with pJIA 2 years to less than 4 years of age. As discussed in Section 16, the Division of Gastroenterology (DG) review team also determined that the Applicant has provided an adequate extrapolation justification for pediatric CD patients 6 years of age and older.

In conclusion, the totality of evidence discussed above and in Section 16 is adequate to justify extrapolating the data and information submitted to the BLA to support a determination of biosimilarity for the indication of polyarticular JIA in patients 2 years of age and older and for the indication of Crohn's disease in adults and pediatric patients 6 years of age and older.

To address the PREA-PMR requirements for these indications and age groups, the Applicant has satisfied the statutory requirements by demonstrating biosimilarity and also provided an adequate scientific justification under the BPCI Act for extrapolating the findings of biosimilarity to the non-studied conditions of use for which the Applicant is seeking licensure and for which US-Humira has been previously approved. The Division of Rheumatology and Transplant Medicine (DRTM) and the DG review teams, as well as the Pediatric Review Committee (PeRC), have determined that the information provided in supplement 10 fulfills the requirements of PMR 3125-1 and PMR 3125-2 as issued at the time of the approval of original BLA.

9. Pediatrics

On September 23, 2016, adalimumab-atto was approved as a biosimilar to US-Humira. Adalimumab-atto was considered to have a new active ingredient and, therefore, PREA applied. At that time, the PREA-required pediatric assessments for pJIA in patients 2 years to less than 4 years of age, pediatric CD in pediatric patients 6 years to 17 years of age, pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age, and development of a presentation to accurately administer adalimumab-atto to pediatric patients who weigh less than 15 kg were deferred.

At the time of the BLA approval, the following PMRs were issued with corresponding due dates as presented below:

PMR #	PMR Details	Final Report Due Date
3125-1	Assessment of Amjevita (adalimumab-atto) for the treatment of Polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 to less than 4 years of age	September 2021
3125-2	Assessment of Amjevita (adalimumab-atto) for the treatment of pediatric Crohn's disease in pediatric patients 6 years to 17 years of age.	September 2021
3125-3	Assessment of Amjevita (adalimumab-atto) for the treatment of pediatric ulcerative colitis in pediatric patients 5 years to 17 years of age	December 2020
3125-4	Develop a presentation that can be used to accurately administer Amjevita (adalimumab-atto) to pediatric patients who weigh less than 15 kg	September 2021

PMRs 3125-1 and 3125-2

In supplement 10, the Applicant provided final reports to fulfill PREA-PMRs 3125-1 and 3125-2. The supplement cross-references the scientific justification submitted with the original BLA for extrapolation.

The DRTM and DG review teams have determined that the Applicant has provided adequate information to fulfill the requirements of PMRs 3125-1 and 3125-2 as issued with the original BLA approval. The submission was reviewed at the FDA PeRC on May 24, 2022. PeRC agreed with the Divisions' assessment and recommendation that the provided information fulfills the intent of PMRs 3125-1 and 3125-2.

PMR 3125-3

On September 8, 2021, a deferral extension was granted for PMR 3125-3 with extension of the final report deadline to February 2028 to align with the expiration of orphan drug exclusivity for US-Humira for pediatric UC 5 years to 17 years of age. PMR 3125-3 remains deferred until February 2028.

PMR 3125-4

In the current submission, the Applicant submitted information (b) (4) (b) (4) to address PREA-PMR 3125-4 (b) (4)

[redacted] A deferral extension request was subsequently granted for PMR 3125-4 on February 28, 2022. PMR 3125-4 remains deferred until December 2022.

The 40 mg/0.8 mL PFS and 20 mg/0.4 mL PFS for adalimumab-atto do not allow for weight-based dosing for pediatric patients who weigh less than 15 kg. However, this does not preclude the use of adalimumab-atto in younger pediatric patients (i.e., 2 to less than 4 years of age who weigh 15 kg or more). According to the Centers for Disease Control and Prevention clinical growth charts[3], the median weights for female and male children 2 years of age is 12 and 12.7 kg, respectively, and 15.9 kg and 16.3 kg, respectively, for children 4 years of age, indicating that the 20 mg/0.4 mL pre-filled syringe could be used in up to half of the pJIA patients in this younger age group.

10. Other Relevant Regulatory Issues

Not applicable.

11. Labeling

Prescribing Information

Revisions in the proposed USPI update the labeling to include the indications of Crohn's disease in pediatric patients 6 to 17 years of age and polyarticular JIA in ages 2 to less than 4 years of age, to include data from associated clinical studies PCD-I and JIA-II, respectively, and to incorporate relevant information, where appropriate, from the US-licensed Humira labeling approved on February 24, 2021 (BLA 125057 supplement 417). Updates to references to Amjevita, adalimumab, and adalimumab products were made for consistency with labeling practice. Table 1 presents a high level summary of the labeling proposal and subsequent interactions between the Applicant and the Agency. Revisions made by the Agency are presented in italics below.

Table 1: Summary of Significant Labeling Changes

Section	Labeling Changes and Discussion
Highlights of Prescribing Information Recent Major Changes	• *FDA recommended not including* [redacted]

[3] https://www.cdc.gov/growthcharts/clinical_charts.htm

Section 1 Indications and Usage	• Revision of existing pJIA indication from “patients 4 years of age and older” to “patients 2 years of age and older.” • Update of existing adult CD indication to “CD” as follows, “treatment of moderately to severely active Crohn’s disease in adults and pediatric patients 6 years of age and older.” Additional revisions of indication statement to remove specific claims for alignment with the reference product. • Revision of indication statement for UC to remove specific claims for alignment with the reference product. • Addition of subheading ‘Limitation of Use’ above statement regarding effectiveness in patients who have lost response to or were intolerant to TNF blockers.

Section 2
Dosage and Administration
	• RA: Addition of 80 mg every other week dose, for alignment with reference product.
	• CD:
	  ○ Removal of statement that use of adalimumab products beyond one year has not been evaluated, for alignment with reference product.
	  ○ Addition of dosing information for pediatric patients with CD
	• Deletion under ‘General Considerations for Administration’ subheading of the statement that, ”The needle cap on the prefilled syringe and on the prefilled autoinjector contains dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex”.
	• *FDA recommended relocating the following statement “The AMJEVITA prefilled syringe and prefilled SureClick autoinjector are not made with natural rubber latex” to Section 16 to align with current labeling practices.*
	• Addition of guidance on missed dose, for alignment with reference product.

Section 6 Adverse Reactions	• Update to listing of clinically significant adverse reactions described elsewhere in labeling, for alignment with reference product.
Section 6.1 Clinical Trials Experience	• Addition of liver enzyme elevation data from an open-label study of adalimumab in patients with pJIA ages 2 years to less than 4 years, for alignment with reference product. • Addition of liver enzyme elevation data from pediatric patients with CD, for alignment with the reference product labeling. • Addition of description of safety in pJIA 2 to less than 4 years of age (Study JIA-II). • Addition of description of safety in CD 6 years to 17 years

	(Study PCD-I).
Section 6.2 Immunogenicity	• Relocation and reformatting of Immunogenicity data to Section 6.2 Immunogenicity for consistency with the reference product labeling.
Section 8.4 Pediatric Use	• Revisions to statements describing pediatric populations in which the safety and efficacy of Amjevita have been established and those in which the safety and effectiveness have not been established. • Addition of description of safety in pJIA 2 to less than 4 years (Study JIA-II) and safety and effectiveness in pediatric Crohn's disease (Study PCD-1).
Section 11 Description	• Inclusion of the specific cell line expression system (e.g., CHO cell line) used to produce Amjevita.
Section 12.3 Pharmacokinetic	• Addition of PK data relevant to the indication of JIA in patients 2 to 4 years of age and in patients with pediatric CD. • Updates to presentation of PK information for consistency with the reference product.
Section 14.2 Juvenile Idiopathic Arthritis	• Addition of description of Study JIA-II in pediatric patients with JIA 2 years of age and older.
Section 14.4 Ankylosing Spondylitis	• *FDA asked the Applicant to change "Humira" to "adalimumab" in the legend for Figure 2.*
Section 14.6 Pediatric Crohn's Disease	• Addition of subsection 14.6 Pediatric Crohn's disease including description of design and efficacy data from Study PCD-I
Section 16	• *FDA indicated that, as required per 21 CFR 201.57(c)(17), the dosage form "injection" should be specified in the reference to "AMJEVITA (adalimumab-atto)".* • *FDA advised the Applicant relocate the following statement from Section 2 to Section 16, "The AMJEVITA prefilled syringe and prefilled SureClick autoinjector are not made with natural rubber latex."* • Deletion of the statement (b) (4) ral (b) (4)
Section 17	• Deletion of the statement: "Advise latex sensitive patients that the needle (b) (4) cap of the prefilled syringe and on the prefilled autoinjector contains dry natural rubber (a derivative of

	latex), which should not be handled by persons sensitive to latex."

Other Labeling

The Applicant proposed to remove reference to "contains dry natural rubber" and to add statements that the PFS and AI are "not made with natural rubber latex" in the Medication Guide, the final printed carton and container labels, and the instructions for use (IFU) for the PFS and AI. Additional updates to the Medication Guide were made for consistency with the reference product labeling. There were also minor editorial revisions proposed for the final printed carton and container labels and IFUs.

Labeling consultants, including OBP-labeling, DMEPA, the Office of Prescription Drug Promotion (OPDP), the Division of Medical Policy Programs (DMPP), have reviewed the submitted labeling and found the proposed revisions acceptable. All labeling changes were agreed upon with the Applicant.

12. Postmarketing Recommendations

There are no new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement or commitment.

13. Risk Evaluation and Mitigation Strategies

The review team did not identify a need for Risk Evaluation and Mitigation Strategies (REMS) to ensure the safe use of adalimumab-atto.

14. Recommended Regulatory Action

Approval.

15. DRTM Designated Signatory Comments

I concur with the team's assessment of the data and information submitted in BLA761024 supplements 10 and (b) (4)

The information submitted in supplement 10 fulfills PREA-required assessments for polyarticular JIA in patients 2 to less than 4 years of age and pediatric Crohn's disease 6 years and older (PMR 3125-1 and PMR 3125-2, respectively, from the approval of original BLA 761024, September 23, 2016). The labeling has been updated to expand

the indications for pJIA to patients 2 years of age and older, and for Crohn's disease to adults and pediatric patients 6 years of age and older. PMR 3125-3 for the assessment of Amjevita (adalimumab-atto) for the treatment of pediatric ulcerative colitis in pediatric patients 5 years to 17 years of age, and PMR 3125-4 for development of a presentation that can be used to accurately administer Amjevita (adalimumab-atto) to pediatric patients who weigh less than 15 kg, remain deferred until February 2028 and December 2022, respectively. No additional data, new PMRs, PMCs, or REMS are required for this supplement.

The proposed labeling changes in labeling supplement 14 to add statements that the PFS and AI "are not made with natural rubber latex" are reasonable.

16. Appendix: Division of Gastroenterology Memo

Amjevita (adalimumab-atto) is currently approved for the treatment of inflammatory bowel disease (IBD) indications of Crohn's disease (CD) and ulcerative colitis (UC) in adults, in addition to other indications.[4] While the CD and UC indications were not directly studied in the adalimumab-atto clinical program, consistent with the principles of the FDA Guidance For Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,[5] the Applicant provided sufficient scientific justification based on the mechanism of action, pharmacokinetics (PK), immunogenicity, and toxicity profile, and sufficient information, including clinical data from the studied populations (healthy subjects, patients with rheumatoid arthritis, and patients with plaque psoriasis), to support licensure of adalimumab-atto for the indications of UC and CD in adults. [6]

At the time of the original BLA application, the Applicant did not seek the licensure of the pediatric CD indication due to pending orphan drug exclusivity. In addition, US-Humira was not licensed for the pediatric UC indication at the time. Thus, the approval letter for BLA 761024, dated 9/23/2016, included the following Pediatric Research Equity Act (PREA) Postmarketing Requirements (PMRs) to address the pediatric IBD indications[7]:

> 3125-2: Assessment of Amjevita (adalimumab-atto) for the treatment of pediatric Crohn's disease in pediatric patients 6 years to 17 years of age.
>
> 3125-3: Assessment of Amjevita (adalimumab-atto) for the treatment of pediatric ulcerative colitis in pediatric patients 6 years to 17 years of age

Since the time of the original approval, the orphan drug exclusivity of US-Humira for

[4] Amjevita USPI accessed on 5/26/2022:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761024s004lbl.pdf
[5] Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015)
[6] Amjevita, Original BLA Division of Gastroenterology Review (9/14/2016)
[7] Amjevita, Approval Letter available at:
https://www.accessdata.fda.gov/drugsatfda docs/appletter/2016/761024Orig1s000ltr.pdf

pediatric CD expired on September 23, 2021. With the submission of BLA 761024/S-010, the Applicant intends to address the PREA PMR for pediatric CD (3125-2) for adalimumab-atto and is seeking the licensure for the pediatric CD indication.

The Applicant did not include the pediatric UC assessment in this supplement. Of note, US-Humira was licensed on February 24, 2021 for the treatment of moderately to severely active UC in pediatric patients 5 years and older. The FDA has determined that US-Humira is eligible for orphan drug exclusivity for pediatric UC, ages 5-17 years. FDA therefore cannot license adalimumab-atto for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028. The Applicant was granted a deferral extension until February 2028 for PMR 3125-3.[8]

The Applicant has provided justification for extrapolating data and information submitted in the application and supplement to support licensure of adalimumab-atto as a biosimilar for the pediatric CD indication for which licensure is sought and for which US-Humira has been previously approved. The Applicant's justification was evaluated and considered adequate, as summarized below:

- Mechanism of Action (MOA)- Similar to the studied indication (plaque psoriasis), TNF-α plays a central role in the pathogenesis of inflammatory bowel disease (IBD , as evidenced by the efficacy of approved TNF-α inhibitors in the treatment of UC and/or CD. In addition to the binding and neutralization of sTNFα, the efficacy of adalimumab in the treatment of IBD is thought to also involve reverse signaling via binding to TNF-α, and other plausible mechanisms of action involving the Fc region of the antibody.[9,10,11] The mechanisms by which adalimumab exerts its therapeutic effect are expected to be the same in adults *vs*. pediatric CD patients. Together with demonstrated structural and functional similarity between adalimumab-atto and US-Humira, the mechanisms of action of adalimumab-atto are not expected to be different from that of US-Humira in pediatric patients with CD, to the extent that the mechanisms are known or can be reasonably determined.

- Pharmacokinetics (PK)- There are no significant differences in the PK characteristics of US-Humira in healthy subjects or across its various approved indications. Adalimumab concentrations are similar in adult vs. pediatric CD patients (Humira USPI, 2021). Together with the data from the original BLA that demonstrated a PK similarity between adalimumab-atto vs. US-Humira vs. EU-Humira in healthy volunteers (Study 20110217), between adalimumab-atto vs. US-/EU-Humira in patients with rheumatoid arthritis (Study 20120262), and between adalimumab-atto vs. US-/EU-Humira in patients with plaque psoriasis (Study 20120263), the PK

[8] The Sponsor submitted a request on 6/8/21 for a deferral extension of the final report submission for PREA PMR 3125-3 from 09/2021 to 02/2028. DG concurred with this request for deferral extension. Refer to clinical review memo by Dr. Sandhya Apparaju filed on August 5, 2021 under BLA 761204 for further details.
[9] Oikonomopoulos A, et al., Current Drug Targets 2013; 14:1421-32.
[10] Tracey D, et al., Pharmacology & Therapeutics 2008; 117:244–79.
[11] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

following adalimumab-atto are not expected to be different to that of US-Humira in pediatric patients with CD.

- Immunogenicity- There is no scientific data or evidence to assume that the mechanisms involved in the development of anti-drug antibodies (ADAs) would differ across indications to preclude extrapolation of immunogenicity data. Immunogenicity rates of US-Humira are comparable between adult and pediatric patients with CD (Humira USPI, 2021). Together with the comparable immunogenicity of adalimumab-atto vs. US-/EU-Humira in healthy volunteers, rheumatoid arthritis patients, and plaque psoriasis patients, the immunogenicity of adalimumab-atto is not expected to be different from that of US-Humira in pediatric patients with CD.

- Safety- The safety profile of US-Humira was comparable in adult vs. pediatric CD patients (Humira USPI, 2021). Together with the data submitted to the original BLA that demonstrated comparable safety profile of adalimumab-atto vs. US-/EU-Humira in adult plaque psoriasis patients (Study 20120263), adult rheumatoid arthritis patients (Study 20122062), and healthy volunteers (Study 20110217), the safety of adalimumab-atto is not expected to be different from that of US-Humira in pediatric patients with CD.

Regulatory Recommendations: The Division of Gastroenterology concludes that sufficient scientific justification was provided to support licensure of adalimumab-atto for the following indication for which the Applicant is seeking licensure:

- The treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

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