

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Arthritis Advisory Committee Meeting
February 9, 2016**

Location: The FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed biologics license application (BLA) 125544, for CT-P13, a proposed biosimilar to Janssen Biotech Inc.'s REMICADE (infliximab), submitted by Celltrion, Inc. The proposed indications (uses) for this product are: (1) 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; (2) reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease; (3) reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; (4) reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy; (5) reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;¹ (6) in combination with methotrexate, reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis; (7) reducing signs and symptoms in patients with active ankylosing spondylitis; (8) reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis; and (9) treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

These summary minutes for the February 9, 2016, meeting of the Arthritis Advisory Committee of the Food and Drug Administration were approved on April 5, 2016.

I certify that I attended the February 9, 2016, meeting of the Arthritis Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/
Stephanie L. Begansky, PharmD
Designated Federal Officer, AAC

_____/s/
Liron J. Caplan, MD
Acting Chairperson, AAC

¹ This indication is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.

**Summary Minutes of the
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February 9, 2016**

The following is a final report of the Arthritis Advisory Committee meeting held on February 9, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Pulmonary, Allergy, and Rheumatology Products and posted on the FDA website at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975.htm>.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Arthritis Advisory Committee (AAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on February 9, 2016, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Celltrion, Inc. The meeting was called to order by Liron Caplan, MD (Acting Chairperson). The conflict of interest statement was read into the record by Stephanie L. Begansky, PharmD (Designated Federal Officer). There were approximately 300 people in attendance. There were 20 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed biologics license application (BLA) 125544, for CT-P13, a proposed biosimilar to Janssen Biotech Inc.'s REMICADE (infliximab), submitted by Celltrion, Inc. The proposed indications (uses) for this product are: (1) 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; (2) reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease; (3) reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; (4) reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy; (5) reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;² (6) in combination with methotrexate, reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis; (7) reducing signs and symptoms in patients with active ankylosing spondylitis; (8) reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis; and (9) treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

² This indication is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.

Attendance:

AAC Members Present (Voting): Mara L. Becker, MD, MSCE; Liron Caplan, MD, PhD (Acting Chairperson); Jeffrey Curtis, MD, MS, MPH; Jennifer Horonjeff, PhD (Consumer Representative); Beth L. Jonas, MD; Donald R. Miller, PharmD, FASHP; Veena K. Ranganath, MD, MS; Eric J. Tchetgen Tchetgen, BS, PhD (via phone); Therese M. Wolpaw, MD, MHPE

AAC Members Not Present (Voting): Andreas M. Reimold, MD

Temporary Members (Voting): Diane Aronson (Patient Representative); Wilma Bergfeld, MD, FAAD; Erica Brittain, PhD; Steve Cramer, PhD; Linda Feagins, MD; Ivan Fuss, MD; Jogarao Gobburu, PhD, MBA, FCP; Eric O. Long, PhD; Donald E. Mager, PharmD, PhD; Mary E. Maloney, MD (via phone); Antonio R. Moreira, PhD; John E. Schiel, PhD; Tor A. Shwayder, MD, LRAM, FAAP, FAAD; Richard M. Siegel, MD, PhD; Steven Solga, MD

Acting Industry Representative to the Committee (Non-Voting): Sean P. Curtis, MD

Designated Federal Officer (Non-Voting): Stephanie Begansky, PharmD

FDA Participants (Non-Voting): Leah Christl, PhD; Badrul Chowdhury, MD, PhD; Nikolay Nikolov, MD; Steven Kozlowski, MD; Kurt Brorson, PhD

Open Public Hearing Speakers: Michael Epstein, MD (Epstein Associates); Seth Ginsberg on behalf of Stephen Marmaras (Global Healthy Living Foundation); Kathleen Arnsten (Lupus and Allied Disease Association); Jay Seigel, MD (Johnson and Johnson); Christine Simmon (Generic Pharmaceutical Association/Biosimilars Council); Lawrence (Larry) LaMotte (Immune Deficiency Foundation); Thair Phillips (RetireSafe); Matthew Banfield on behalf of Michael Werner (Biosimilars Forum); Dolottie Layton; Gregory Schimizzi; Liz Smith (Arthritis Foundation); Angus Worthing, MD (American College of Rheumatology); Bernadette Eichelberger (Academy of Managed Care Pharmacy, Biologics and Biosimilars Collective Intelligence Consortium); Harry Gewanter, MD (Alliance for Safe Biologic Medicines); Joshua Stalow, MD (Alliance for Patient Access); Gideon Smith, MD (American Academy of Dermatology Association); Cindy Becker; Sarah Buchanan (Crohn's and Colitis Foundation of America); Andrew Spiegel (Global Colon Cancer Center); Paul Melmeyer (National Organization of Rare Disorders)

The agenda was as follows:

Call to Order and Introduction of Committee

Liron Caplan, MD, PhD
Acting Chairperson, AAC

Conflict of Interest Statement

Stephanie L. Begansky, PharmD
Designated Federal Officer, AAC

FDA OPENING REMARKS

Janet Woodcock, MD
Director, CDER, FDA

Overview of the Regulatory Pathway and
FDA's Guidance for the Development and
Approval of Biosimilar Products in the US

Leah Christl, PhD
Associate Director, Therapeutic Biologics
Therapeutic Biologics and Biosimilars Staff
Office of New Drugs (OND)
CDER, FDA

Clarifying Questions

Introductory Remarks

Nikolay P. Nikolov, MD
Clinical Team Leader
Division of Pulmonary, Allergy & Rheumatology
Products (DPARP)
Office of Drug Evaluation II (ODE-II)
OND, CDER, FDA

APPLICANT PRESENTATIONS

CELLTRION, Inc.

Introduction

Elizabeth Pollitt, PhD
Vice President
Head of CMC for Regulatory Affairs
CELLTRION, Inc.

Physicochemical and
Functional Studies

Elizabeth Pollitt, PhD

Nonclinical Studies

Elizabeth Pollitt, PhD

Clinical Review:
Pharmacology, Immunology, Efficacy and
Safety

Alex Kudrin, MD, PhD, MBA
Vice President, Head of Clinical Development
CELLTRION, Inc.

Totality of Evidence

Alex Kudrin, MD, PhD, MBA

CT-P13 Use in Patients with IBD: Post-
Marketing Clinical Studies and
Real-World Experience

Peter Laszlo Lakatos, MD, DsC
Associate Professor
Head of Gastroenterology/Hepatology Unit and
Endoscopy
Semmelweis University
Budapest, Hungary

Totality of Evidence of CT-P13:
Clinical Perspective

Vibeke Strand, MD, MACR, FACP
Adjunct Clinical Professor Division of
Immunology/Rheumatology
Stanford University

Clarifying Questions

BREAK

FDA PRESENTATIONS

CT-P13 Product Quality Review

Kurt Brorson, PhD
Product Quality Team Leader
Division of Biotechnology Research and Review 2
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ), CDER, FDA

CT-P13 Statistical Equivalence
Testing for Bioactivity

Meiyu Shen, PhD
CMC Statistical Reviewer
Division of Biometrics VI, Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA

Clinical Pharmacology Review

Lei He, PhD
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology II
Office of Clinical Pharmacology (OCP)
OTS, CDER, FDA

Clinical Efficacy Review

Gregory Levin, PhD
Mathematical Statistician
Division of Biometrics II, OB, OTS, CDER, FDA

Clinical Safety and Immunogenicity Review

Juwaria Waheed, MD
Medical Officer
DPARP, ODE-II, OND, CDER, FDA

Considerations for Extrapolation of
Biosimilarity

Nikolay P. Nikolov, MD

Clarifying Questions for FDA

LUNCH

OPEN PUBLIC HEARING

BREAK

CHARGE TO THE COMMITTEE

Nikolay P. Nikolov, MD

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Does the Committee agree that CT-P13 is highly similar to the reference product, US-licensed Remicade, notwithstanding minor differences in clinically inactive components?

Committee Discussion: Overall, the committee indicated that CT-P13 does seem to be highly similar to the reference product. One panel member expressed that there is uncertainty about

the glycoform differences and the effect on fragment crystallizable (Fc) receptors and antibody-dependent cellular cytotoxicity (ADCC). There were also questions raised regarding the missing data in the clinical studies and how that may impact the result from the clinical studies. One member stated that there are some analytical differences in the products (e.g. average levels of aggregates or charge isoforms). The member was unsure if they were clinically inactive components in terms of impact on clinical outcome, but noted that they were at levels comparable to other biotechnology products. Another panel member stated that with some of the highly complex assays, it would have been nice to have actual values rather than just averaged or normalized results. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Does the Committee agree that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied conditions of use (rheumatoid arthritis (RA) and ankylosing spondylitis (AS))?

Committee Discussion: In general, the committee indicated that there were no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied conditions of use (RA and AS). One committee member raised a question about the similarity margin used. Other committee members stated that despite the evidence, there is still uncertainty about multiple switching between the biosimilar and the reference product from both the patient and provider perspectives. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Does the Committee agree that there is sufficient scientific justification to extrapolate data from the comparative clinical studies of CT-P13 in RA and AS to support a determination of biosimilarity of CT-P13 for the following additional indications for which US-licensed Remicade is licensed (psoriatic arthritis (PsA), plaque psoriasis (PsO), adult and pediatric Crohn's disease (CD), and adult and pediatric ulcerative colitis (UC)³)? If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

Committee Discussion: The overall consensus of the committee was that there was adequate scientific justification to support extrapolation of the data from comparative clinical studies in RA and AS to support a determination of biosimilarity of CT-P13 for the additional indications. However, there was some reservation amongst the committee relating to extrapolation of the data to Crohn's Disease, Ulcerative Colitis and specifically pediatric Ulcerative Colitis due to the limited clinical data in these indications. Some committee members suggested that additional clinical trials should be done in these populations, while others pointed out that the point of the 351(k) approval pathway would be compromised if these additional studies were required. Several committee members stated that the benefits of

³ Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. Although FDA is interested in the Committee's views regarding the scientific justification for extrapolating clinical data to support a determination of biosimilarity for CT-P13 for this indication, FDA is not asking the Committee to vote on licensure of CT-P13 for pediatric ulcerative colitis because FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

extrapolation to society as a whole, in terms of access, were worth the perceived risks of extrapolation. Please see the transcript for details of the committee discussion.

4. **VOTE:** Does the Committee agree that based on the totality of the evidence, CT-P13 should receive licensure as a biosimilar product to US-licensed Remicade for each of the indications for which US-licensed Remicade is currently licensed and CT-P13 is eligible for licensure (RA, AS, PsA, PsO, adult CD, pediatric CD, adult UC)?

Vote Result: Yes = 21 No = 3 Abstain = 0

- a. **DISCUSSION:** Please explain the reason for your vote. If you voted no, explain whether this was applicable to all or some of the indications and why.

***Committee Discussion:** The majority of the committee voted “Yes”, agreeing that based on the totality of the evidence, CT-P13 should receive licensure as a biosimilar product for each of the indications for which it is eligible. The committee as a whole stated that the total package showed a large number of analytical techniques proving that the threshold for overall biosimilarity had been met. One committee member noted that even though there are some residual concerns with extrapolation, it was worth taking the risk to provide new products that may reduce the cost of bringing drugs to the market and in turn may have a reduced cost to patients since the evidence of biosimilarity was compelling. The committee members who voted “No” were primarily concerned with the extrapolation to the Crohn’s Disease, Ulcerative Colitis and pediatric Ulcerative Colitis indications due to the limited clinical data in these indications and the ongoing study in IBD. Concerns were also expressed by the consumer representative that the introduction of biosimilars would need more education to the community and to patients to provide more confidence in these products. Please see the transcript for details of the committee discussion*

The meeting was adjourned at approximately 5:10 p.m.