CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761349Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 012678

MEETING MINUTES

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Jake Myhill, PharmD, MBA
Senior Global Program Regulatory Manager

Dear Dr. Myhill:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for secukinumab (AIN457).

We also refer to the telecon between representatives of your firm and the FDA on December 8, 2021. The purpose of the meeting was to discuss 16-week data from study CAIN457P12302 and obtain pre-submission advice for the new intravenous formulation.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Susie Choi, Regulatory Project Manager, at 240-402-2925.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, M.D.
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

[1]We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: December 8, 2021 at 1:05 PM-1:55PM ET
Meeting Location: Teleconference

Application Number: 012678
Product Name: secukinumab (AIN457)

Indication: Psoriatic Arthritis
Sponsor Name: Novartis
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Nikolay Nikolov, MD
Meeting Recorder: Susie Choi, PharmD

FDA ATTENDEES

Nikolay Nikolov, MD, Director, Division of Rheumatology and Transplant Medicine (DRTM)
Raj Nair, MD, Clinical Team Leader, DRTM
Amit Golding, MD, PhD, Clinical Reviewer, DRTM
Steve Leshin, PhD, Pharmacology/Toxicology Reviewer, Division of Pharmacology Toxicology for Immunology & Inflammation
Jianmeng Chen, MD, PhD, Clinical Pharmacology Team Leader, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP)
Jing Niu, MD, Clinical Pharmacology Reviewer, DIIP, OCP
Youwei Bi, PhD, Pharmacometrics Team Leader, Division of Pharmacometrics, OCP
Anjali Shukla, PhD, Product Quality Team Lead, Division of Biotechnology Review and Research II (DBRRII), Office of Biotechnology Products (OBP), Office of Pharmaceutical Quality (OPQ)
Qiong Fu, PhD, Product Quality Reviewer, DBRRII, OBP, OPQ
Rebecca Rothwell, PhD, Biostatistics Team Leader, Division of Biometrics III, Office of Biostatistics (OB)
Hongling Zhou, PhD, Biostatistics Reviewer, Division of Biometrics III, OB
Susie Choi, PharmD, Regulatory Project Manager, Division of Regulatory Operations, Immunology and Inflammation (OII), for DRTM
Emily Gotschlich, MD, Clinical Reviewer, DRTM

SPONSOR ATTENDEES

Abhijit Bapat, Clinical Development Medical Director

Gerard Bruin, Director, Pharmacokinetics
Thomas Dumortier, Senior Director Pharmacometrics
Gregory Ligozio, Head Biostatistics Immunology Hepatology & Dermatology
Alain Marti, Global Program Head
Ruvie Martin, Associate Director Biostatistics
Meni Melek, Head Regulatory Affairs Immunology Hepatology & Dermatology
Jelena Mijatovic, Global Program Regulatory Director
Jake Myhill, Senior Global Program Regulatory Manager
Kristine Ogozalek, Global Therapeutic Area Lead
Kelly Ohlinger, Regulatory Affairs Fellow
Brian Porter, Clinical Development Head Immunology Hepatology & Dermatology
Luminita Pricop, Global Program Clinical Head
Nicole Mahoney, Executive Director US Regulatory Policy
Ignacio Rodriguez, Global Head Medical Safety
Angelika Jahreis, Development Unity Head Immunology Hepatology & Dermatology
Oluwadamilola Soyemi, US Disease Area Head Rheumatology
Malcolm Henderson, Regulatory Affairs CMC Biologics Portfolio Head

1.0 BACKGROUND

Novartis is seeking pre-submission advice for intravenous formulation of secukinumab. A meeting request was submitted on October 1, 2021. A teleconference was granted on October 22, 2021. Novartis' questions from the briefing package, dated November 8, 2021, are provided below in italics, followed by FDA responses.

FDA sent Preliminary Comments to Novartis on December 6, 2021.

2.0 DISCUSSION

Introductory Comments:

With data obtained from Study CAIN457P12302 (P12302), you propose to submit an application for a secukinumab intravenous (IV) loading dose of 6 mg/kg at Week 0 followed by a secukinumab IV maintenance dose of (b)(4) mg/kg every 4 weeks as a new dosing regimen for the psoriatic arthritis (PsA) indication. We have the following comments for your consideration:

Based on the submission (section 4.1), the Ctrough for the proposed IV dosing regimen is comparable to that of the 300 mg Q4W subcutaneous (SC) dosing regimen, the higher of the two approved SC regimens. However, the proposed IV dosing regimen appears to also result in higher Cmax and AUC than the 300 mg Q4W SC dosing regimen.

Further, all the pharmacokinetic (PK) parameters are estimated to be even higher than the initial approved SC dosing regimen in PsA, 150 mg Q4W. Based on the estimated differences between the SC and IV dosing regimens' PK parameters, we are concerned

that your proposed IV loading/maintenance dosing regimen may not have sufficient safety information to support the benefit-risk assessment with this dosing regimen, particularly for more rare and latent adverse events. We note that the short-term placebo-controlled comparisons from Study CAIN457P12302 are not likely to address these concerns. The interpretability of the open-label and uncontrolled data from the long-term extension of Study CAIN457P12302 is limited to inform regulatory decisions on safety.

Further, while Study CAIN457P12302 may be adequately designed to assess the efficacy of the proposed IV regimen proposed in PsA, it appears that the efficacy observed on the primary and multiple secondary endpoints was in the plateau of the exposure-response curve, i.e. not offering additional benefit even at the higher Cmax and AUC with the proposed IV dosing regimen. This is an important consideration in the benefit-risk assessment of this new dosing regimen.

Given the above considerations, the data proposed for submission may not be sufficient to support the adequate benefit-risk assessment of the proposed IV dosing regimen in PsA.

To address these uncertainties, we recommend an alternative approach. We note that secukinumab is currently approved for PsA with a two-tiered SC dosing regimen: a 150 mg Q4W and for patients who continue to have active PsA, a 300 mg Q4W. This would allow for leveraging both safety and efficacy information from these two dosing regimens if you can identify a lower IV dosing regimen(s) that would better approximate both approved SC dosing regimens to result in similar pharmacokinetic parameters. For example, you can target lower IV doses at the same Q4W interval, with Cmax ≤ the 300 mg SC dose; Ctrough ≥ the 150 mg SC dose; AUC in the range of 150 mg SC and 300 mg SC doses). The estimated exposures with the lower IV dosing regimen can be confirmed in a PK study. This approach will better support an IV dosing regimen(s) that can leverage relevant safety information from the currently approved SC dosing regimens, for which the benefit-risk has been established, without the need for comparative long-term safety assessments. Using this approach, efficacy can be extrapolated, with appropriate justification, from the efficacy established with the SC dosing regimens. Also, refer to the February 12, 2019 EOP2 meeting responses and discussion on the considerations for the selection of the IV dosing regimen.

Discussion to Introductory Comments:

1. PK parameters
    a. Novartis: Prior data from secukinumab development program (handout) with 10 mg/kg IV loading doses followed by 150 SC showed no significant increase in safety risk; data provided from study P12302 with IV 6/3 mg/kg IV shows lower exposure than 10mg/kg IV loading and achieved similar exposure to 300 mg SC dosing regimen. Cmax for IV 6/3 mg/kg is admittedly higher than 300 mg SC regimen, but Cmax is more relevant to acute risk, e.g. infusion reactions, which were not observed during study

P12302.

b. DRTM: PK parameters such as Cmax, AUC, Ctrough, and Caverage are highly correlated and there are no data to conclude that Cmax is not related to chronic AEs; the long-term exposure/response for safety is based on prior data with 150/300 mg SC; current exposure with the (b) (4) is higher than currently approved (especially the 150 mg SC starting dose) limiting the reliance on the long-term safety data with the currently approved dosing regimens. The potential for increased safety risks associated with higher long-term immunosuppression with the higher exposure seen with the 3 mg/kg regimen is unknown. The Division reiterates that a preferred exposure from chronic IV dosing would have a Cmax no higher than 300 mg SC dose, Ctrough greater than or equal to 150 mg SC dose, and AUC intermediate between 150 and 300 mg SC doses.

2. Benefit: Risk assessment
   a. Novartis: The 6/3 mg/kg IV exposure approximates the 300 mg SC regimen; prior data showed that 300 mg SC regimen is superior to 150 mg SC regimen; study P12302 was not designed to show added benefit of the higher exposure with IV dosing.

   b. DRTM: The higher approved dose of 300 mg SC is reserved for patients who do not respond to the initially approved dose of 150 mg SC; as the efficacy results of study P12302 do not appear to show an added benefit over the 150 mg SC dose, there needs to be adequate confidence that the IV dosing regimen has similar long-term safety in order to justify a benefit: risk that is favorable for the IV dosing regimen.

3. Max dose cap
   a. Novartis: (b) (4) (b) (4) For safety, it would be reasonable to cap the maximum IV dose at 300 mg similar to the maximum approved dose of 300 mg SC.

   b. DRTM: In general, there should be a cap on absolute dose for body weight based dosing regimens, to avoid overdose in patients with very high body weight. (b) (4)

4. PK Bridging/MIDD approach
   a. Novartis: They are open to MIDD approach and would like to know if prior safety data with higher Cmax/AUC exposures could be leveraged and used in a Modeling approach to support safety of the proposed IV dosing regimen.

b. DRTM: It is at sponsor's discretion whether to propose a PK modeling approach, however a confirmatory PK study of IV doses may be needed. There is also a consideration that an IV dosing regimen that more closely matches the exposures of the approved doses could allow for approval of an IV regimen for multiple indications, not just PsA. In this context, the Agency advised that the sponsor to consider presenting several approaches, including the detailed study design for the PK study, and submitting their proposal under the MIDD pilot.

c. Novartis: For the dose selection of a lower IV dose, the sponsor also asked if the Cmax of the proposed dosing regimen could slightly exceed the point estimate of the SC 300 mg dosing regimen, but is still "within the range".

d. DRTM: For dose selection of a lower IV dose, FDA encouraged the sponsor to estimate the PK profile of different IV doses based on PK simulation and present the work at the MIDD meeting. The details of dose selection based on the modeling approach can be submitted in the proposal for the MIDD pilot submission.

Question 1:
Does the Agency agree that the data obtained from Study CAIN457P12302 support registration of the new formulation with the proposed i.v. dosing regimen for the indication treatment of active PsA in adults under new BLA?

FDA Response to Question 1:
Refer to the Introductory Comments.

Discussion to Question 1:
Refer to discussion of introductory comments.

Question 2:
Does the Agency agree with the proposed content of Modules 1, 2, 3 and 5?

FDA Response to Question 2:
Refer to the Introductory Comments. If you can address the concerns in the Introductory Comments, the proposed contents of Modules 1, 2, 3, and 5 appear reasonable. Cross-referencing to the original BLA for Module 4 is also reasonable.

Discussion to Question 2:
Refer to discussion of introductory comments.

Question 3:

A) Does the Agency agree with the proposed presentation of the efficacy data for PsA that will be submitted in the Summary of Clinical Efficacy (SCE; CTD section 2.7.3) to support the approval of secukinumab for i.v. administration for the treatment of adults with active PsA under new BLA?

B) Does the Agency agree that a separate integrated summary of efficacy (ISE) will not be needed, as the information required in the ISE will be in the SCE and SCE Appendices?

FDA Response to Question 3:

A) Refer to the Introductory Comments. If you can address the concerns in the Introductory Comments, your approach is reasonable.

B) Refer to the Introductory Comments. If you can address the concerns in the Introductory Comments, your approach is reasonable, provided all required information on the integrated efficacy analyses is appropriately cross-referenced.

Discussion to Question 3:

Refer to discussion of introductory comments.

Question 4:

A) Does the Agency agree that the proposed safety data and extent of patient exposure that will be submitted in the Summary of Clinical Safety (SCS; CTD section 2.7.4) are sufficient to support the approval of secukinumab for i.v. administration for the treatment of adults with active PsA under new BLA?

B) Does the Agency agree that a separate integrated summary of safety (ISS) will not be needed, as the information required in the ISS will be in the SCS and SCS Appendices?

FDA Response to Question 4:

A) Refer to the Introductory Comments. If you can address the concerns in the Introductory Comments, your approach is generally reasonable. However, the meeting package indicates that within the SCS, the Week 16 safety data from study CAIN457P12302 will be compared side-by-side with the Week 16 safety data from pooled PsA studies (CAIN457F2312, CAIN457F2318, CAIN457F2336 and CAIN457F2342) in order to demonstrate the comparability of the safety of IV regimen and SC regimen for PsA populations. It is not clear how this pooling will be performed given the differences in design and treatment arms across these four studies.

B) Refer to the Introductory Comments. If you can address the concerns in the Introductory Comments, your approach is reasonable, provided all required

information on the integrated safety analyses is appropriately cross-referenced.

Discussion to Question 4:
Refer to discussion of introductory comments.

Question 5:
Does the Agency agree that the proposed pharmacokinetic data that will be submitted in the Summary of Clinical Pharmacology (SCP; CTD section 2.7.2) are sufficient to support the approval of the proposed secukinumab i.v. dosing regimen for the treatment of adults with active PsA?

FDA Response to Question 5:
Refer to the Introductory Comments. If you can address the concerns in the Introductory Comments, we have the following comment: You propose a weight-based dosing regimen for IV administration. We note that the exposures of secukinumab tend to be higher in patients with very high bodyweight (Figure 4-6). We recommend that you include a maximum absolute dose for the IV dosing regimen (e.g., 300 mg IV).

Discussion to Question 5:
Refer to discussion of introductory comments.

Question 6:
Does the Agency agree with the proposed contents of the 120-Day Safety Update?

FDA Response to Question 6*:*
Refer to the Introductory Comments. If you can address the concerns in the Introductory Comments, your proposal is reasonable.

Discussion to Question 6:
Refer to discussion of introductory comments.

Question 7:
Does the Agency agree with the proposal for submission of patient narratives from the study along with the associated Case Report Forms (CRFs)?

FDA Response to Question 7:
If you can address the concerns in the Introductory Comments, your proposal for submission of patient narratives along with the associated CRFs is reasonable.

Discussion to Question 7:
Refer to discussion of introductory comments.

Question 8:

Does the FDA agree with the proposed plan for submission of dataset and programs for the new secukinumab BLA?

FDA Response to Question 8:

Refer to the Introductory Comments. If you can address the concerns in the Introductory Comments, the proposed plan for submission of dataset and programs is acceptable.

Discussion to Question 8:

Refer to discussion of introductory comments.

Question 9:

Does the Agency agree with the submission of a full waiver request for secukinumab for pediatric studies in patients aged 0 to 17 years, as described in the agreed iPSP?

FDA Response to Question 9:

We acknowledge that you have an agreed iPSP for the IV formulation that includes your plan on requesting a full waiver for PREA-required studies for PsA.

We also acknowledge that the PREA requirements for PsA have, in the past, been waived with the justification that studies in juvenile PsA have been impossible or highly impracticable because there are too few children with the disease/condition to study.

We note that the justification supporting the default waiver has been based on the assumption that adequate and well-controlled studies were needed to address PREA requirements for PsA, which would have made such studies impracticable, even though there are pediatric patients with PsA.

However, based on the evolving understanding of the high degree of similarity of the disease between adults and pediatric patients with PsA[2] and the considerations of a pharmacokinetic (PK)-matching and extrapolation of efficacy from adults to pediatric patients, the Division considers that such studies are possible. Respectively, we recommend that you submit an amended iPSP to address PREA in JPsA. We further note that your sBLA for secukinumab for SC administration is currently under review for the indication of juvenile psoriatic arthritis (JPsA) in patients age 2 to <17 years old. Data from this program could further inform your amendment to the iPSP.

The amended iPSP should be clearly labeled as an amended iPSP. For additional details, see **PREA REQUIREMENTS** below.

[2] 2019 FDA Workshop: Accelerating drug development for polyarticular juvenile idiopathic arthritis (https://cersi.umd.edu/accelerating-drug-development-polyarticular-juvenile-idiopathic-arthritis-pjia)

Discussion to Question 9:
Refer to discussion of introductory comments.

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[3] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the

[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[7]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of

[7] https://www.fda.gov/media/85061/download

information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

5.0 ACTION ITEMS

N/A

6.0 ATTACHMENTS AND HANDOUTS

Novartis' response to FDA's preliminary comments.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NIKOLAY P NIKOLOV
01/14/2022 12:28:42 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 12678

MEETING MINUTES

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Jake Myhill, PharmD
Global Program Regulatory Manager, Regulatory Affairs

Dear Dr. Myhill:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AIN457 (secukinumab).

We also refer to the meeting between representatives of your firm and the FDA on February 12, 2019. The purpose of the meeting was to discuss the Phase 3 development program for secukinumab for the indications of PsA and Ax-SpA with an IV treatment regimen.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 348-1896.

Sincerely,

{See appended electronic signature page}

Ngoc-Linh Do, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: February 12, 2019; 3:00 – 4:00 PM
Meeting Location: Building 22, Conference Room 1311

Application Number: 012678
Product Name: AIN457 (secukinumab)

Indication: Psoriatic arthritis and axial spondyloarthritis
Sponsor: Novartis Pharmaceuticals Corporation

Meeting Chair: Nikolay Nikolov, MD
Meeting Recorder: Ngoc-Linh Do, PharmD

FDA ATTENDEES

Nikolay Nikolov, MD, Supervisory Associate Director for Rheumatology, DPARP
Raj Nair, MD, Clinical Reviewer, DPARP
Lei Nie, PhD, Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Cesar Torres, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Anshu Marathe, PhD, Clinical Pharmacology Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Dipak Pisal, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Steve Leshin, PhD, Pharmacology/Toxicology Reviewer, DPARP
Anjali Shukla, PhD, Product Quality Reviewer, Division of Biotechnology Review and Research II (DBRRII), Office of Biotechnology Products (OBP), Office of Pharmaceutical Quality (OPQ)
Ngoc-Linh Do, PharmD, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Yogita Bahl, Director Regulatory, CMC Biologics
Abhijit Bapat, Clinical Development Medical Director
Greg Ligozio, Global Group Head BSS
Meryl Mendelson, Senior Global Program Clinical Head
Shephard Mpofu, Senior Global Program Head
Jake Myhill, Global Program Regulatory Manager
Kristine Ogozalek, Global Therapeutic Area Lead
Jorge Safi, Senior Global Program Safety Lead

Gretchen Trout, Policy and FDA Liaison
Neila Benabadji, Global Program Regulatory Director
Thomas Dumortier, Director Pharmacometrics
Tingting Zhuang, Principal Biostatistician

1.0 BACKGROUND

Novartis submitted an End-of-Phase 2 meeting on November 19, 2018 to discuss secukinumab IV formulation for the indications of PsA and Ax-SPA. On January 8, 2019, the Division sent the Preliminary Comments to Novartis and on January 11, 2019 Novartis communicated to the Division requesting to focus the discussion on the Preliminary Comments and questions 1 through 5.

The questions from the briefing package are in *italics,* followed by FDA responses in normal font, and meeting discussion in bold.

2.0 QUESTIONS AND RESPONSES

FDA Introductory Comments:

You have developed a new secukinumab drug product, liquid in vial (LIV) formulation, for a new, intravenous (IV), route of administration which will be developed to support a new BLA with new labeling and brand name. You propose to support this program with two clinical studies, one in axial spondyloarthritis (CAIN457P12301) and one in psoriatic arthritis (CAIN457P12302) where patients will receive 10 mg/kg loading dose with your LIV formulation at weeks 0, 4, and 8 and then be dosed chronically every 8 weeks. You have proposed that primary efficacy assessment will be at Week 16 for both of your proposed studies. We have the following comments regarding this proposal:

1) We note that your proposed IV dosing regimen appears to provide higher concentrations of secukinumab as compared to the currently approved high subcutaneous dosing with load of 300 mg. As the exposures with this regimen will provide exposures significantly higher than the currently recommended starting 150 mg and alternative 300 mg dose for psoriatic arthritis and the currently recommended dose of 150 mg for ankylosing spondylitis, we are concerned about the impact of this higher exposure on safety, including long-term safety. Importantly, it is unclear if the higher exposure would result in any increased benefit compared to the subcutaneous dosing regimen given that these exposures are likely to be on the plateau of the exposure-response curve. Further, there does not appear to be an adequate dose exploration with the IV route of administration to support the proposed dosing regimen. Thus, the assessment of the benefit-risk of the proposed dosing regimen may be challenging.

   To address these comments, we recommend that you consider including an active comparator in the proposed studies for blinded longer-term comparative assessment of efficacy and, importantly safety, that will be needed to inform the benefit-risk of the currently proposed IV dosing regimen and inform labeling considerations. Because we

do not anticipate the use of a placebo for one year in these patient populations, we recommend that your trials include an approved active control arm. A safety database of size and duration to provide a substantive comparative assessment of safety between the proposed IV dosing regimen and the comparator will be expected. The adequacy of the safety database will also depend on the overall benefit-risk of the proposed dosing regimen.

Alternatively, you may consider using an IV dosing regimen(s) that will approximate both approved SC dosing regimens to better support an IV dosing regimen that can leverage relevant safety information from the currently approved SC dosing regimens without the need for comparative long-term safety assessments.

2) We note that assessment of efficacy at Week 16, as currently proposed, will likely be significantly impacted by the very high exposures from the proposed IV loading and are not likely to reflect the true long-term efficacy of this dosing regimen. Thus, we recommend that your clinical program is conducted without the IV loading.

Discussion

The Sponsor's rationale for the proposed dosing regimen of (b) (4) (b) (4) was that C_{min} is the driver of efficacy and that the proposed dose will deliver an average patient a C_{min} that matches the C_{min} of the high SC dosing regimen.

The Division expressed potential safety concerns with the proposed dose, as the proposed IV dose is much higher than either of the approved SC doses of secukinumab, and without a dose ranging study for the IV formulation it is difficult to evaluate if the proposed regimen is an optimal dose regimen. The Division re-iterated that there are limited long-term safety data for the proposed IV dosing, and exposing patients to a much higher dose than the currently approved SC regimen for psoriatic arthritis and ankylosing spondylitis poses a safety concern which may need to be taken into consideration in the overall benefit-risk assessment. Alternatively, if the IV regimen has an exposure comparable to that of the SC regimen, then it may be possible to leverage safety data from studies evaluating the SC regimen, and the studies may only need to demonstrate efficacy, and a long-term study to evaluate rare adverse events or adverse events with long latency periods may not be needed.

The Division also expressed concerns with the study's proposed 16-week efficacy endpoint. Specifically, it would be difficult to evaluate long-term efficacy at that timepoint, as the proposed timepoint of assessment will likely reflect the impact of high initial exposure to secukinumab with the loading dose, rather than the effect of chronic dosing.

Novartis inquired if an active control would be needed, if the IV regimen exceeded the approved SC regimens. The Division advised that controlled long-term safety data with the IV regimen of at least one year of data would be needed, which would be better informed by comparison to an active comparator. The choice of an active comparator would be at the discretion of the Sponsor. Novartis asked if a biosimilar would be acceptable as an

active control, and the Division relayed that use of a biosimilar product could be acceptable but additional information may be needed depending on the specifics of the proposal, i.e. US- vs. non-US-licensed biosimilar product.

The Sponsor proposed two potential solutions to assessing efficacy at 16 weeks in the proposed IV studies. One proposal was to study a secukinumab arm without a loading dose. The second proposal was to study a dose arm that has a higher dose at week 0 but then is followed by every 8-week dosing. The Division stated that either solution could be appropriate.

Novartis asked if a large patient population would be needed to support safety in the active-controlled study. The Division relayed that a study should be of sufficient size and duration to allow for the assessment of rare, or latent serious safety events.

Novartis inquired if IV dosing regimen exposure were to approximate the SC regimen, could a single study in a single indication be sufficient to extrapolate to other indications. The Division advised that, in the context of a new BLA with separate labeling, the product will likely be labeled with what was studied, i.e. with the data generated from the IV program. However, the Division clarified that given the prior knowledge about secukinumab, a single study for each indication would be reasonable. Such study(ies) can be of short duration, i.e. 12 to 16 weeks, sufficient to demonstrate efficacy.

Question 1
Does the Agency agree with the proposed trial design and endpoints for Studies CAIN457P12302 in PsA and CAIN457P12301 in axSpA?

Question 1a
Does the Agency agree with the proposed trial design and endpoints for Study CAIN457P12302 in PsA?

FDA Response
Please see our Introductory Comments regarding the trial design considerations. In addition, we recommend that the primary endpoint is consistent with the endpoint used to support the approval of the original indication, i.e. ACR20. You may consider ACR50 and ACR70 as secondary endpoints, which can be described in the product labeling, if supported by adequate data and appropriate analyses.

Some of the other secondary endpoints you are proposing may represent overlapping and ancillary benefits with respect to the core outcome measures. Note that redundant efficacy information/claims may not be considered appropriate for inclusion in labeling, even if those claims are supported by adequate instruments and an adequate statistical approach.

Question 1b
Does the Agency agree with the proposed trial design and endpoints for Study CAIN457P12301 in axSpA?

FDA Response
Please see our Introductory Comments regarding the trial design considerations.

With respect to the primary endpoint, we recommend that the primary endpoint is consistent with the endpoint used to support the approval of the ankylosing spondylitis indication, i.e. ASAS20. You may consider ASAS40 as a secondary endpoint, which can be described in the product labeling, if supported by adequate data and appropriate analyses.

With respect to the proposed use of MRI, we have the following comments. The information you have submitted thus far is not sufficient to justify the use of MRI assessment results to support the labeling claims in question. While we acknowledge the motivation for assessing structural damage progression using new approaches and modalities such as MRI, there is no regulatory precedent for using these endpoints or instruments. An adequate justification of the appropriateness of a biomarker endpoint (such as MRI) will include sufficient evidence that an effect on this candidate surrogate endpoint will reliably predict an effect on the clinical outcomes of interest. Simply providing evidence of a correlation is not sufficient. Furthermore, you should be able to provide and justify the magnitude of difference on the biomarker endpoint that is necessary to reliably predict a meaningful effect on the clinical outcomes of interest. Finally, any additional proposed claims should provide unique and important information, i.e., the effect on the biomarker should intend to predict an effect on some unique patient outcome, such as long-term loss of function or disability. In that light, the relevance of correlations between MRI assessments and short-term (e.g., over 6 months or 1 year) symptoms and function is unclear.

We note that adequately designed 24-week, or longer, active control studies with no crossover of patients initially assigned to the active comparator may provide data to inform the treatment effect of structural progression using the established X-ray endpoints.

Some of the other secondary endpoints you are proposing may represent overlapping and ancillary benefits with respect to the core outcome measures. Note that redundant efficacy information/claims may not be considered appropriate for inclusion in labeling, even if those claims are supported by adequate instruments and an adequate statistical approach.

Discussion on Question 1a and 1b
Novartis clarified their rationale for utilizing the primary endpoints of ACR50 and ASAS40. The Sponsor explained that the field has evolved in the expectation of clinical endpoints, and commented that physicians and patients expect higher hurdle, clinically meaningful outcomes.

The Division acknowledged that the ASAS40 and ACR50 endpoints are reasonable, but advised that the recommendation of ASAS20 and ACR20 were for the purpose of remaining consistent with the primary approval of secukinumab. Provisions should be made in the statistical analysis plan so that all endpoints considered for labeling can be evaluated.

Question 2
Does the Agency find the proposed dose regimen reasonable?

FDA Response
We do not agree. See our Introductory Comments.

Discussion
See meeting discussion for the Introduction Comment.

Question 3
Does the Agency agree that the size and duration of the proposed studies are sufficient to support the filing of a new BLA for iv formulation of secukinumab in the indications of PsA and axSpA?

FDA Response
We do not agree. See our Introductory Comments.

Discussion
See meeting discussion for the Introductory Comments.

Question 4
Does the Agency agree that (b) (4) (b) (4) *to the future label of the secukinumab iv formulation?*

FDA Response
At this time, we cannot agree with this proposal. You intend to submit a new BLA with a new labeling and brand name. The labeling is likely to reflect the clinical data supporting this product. See also our Introductory Comments.

Discussion
Novartis inquired if the Division was opened to the concept of (b) (4) **The Division clarified that it cannot comment further at this time.**

Question 5
Does the Agency agree that this (b) (4) *approach appears reasonable, assuming the indication is approved in the Cosentyx label?*

FDA Response
It is premature to discuss labeling of nr-AxSpA given that the SC program is ongoing and the benefit-risk of secukinumab has not been characterized in this indication. See also our Introductory Comments and response to Question 4.

Discussion
Novartis asked if the Division agreed that studying a total axSpA population would allow for labeling an indication of axSpA. The Division advised that is it premature to discuss labeling for axSpA until there is more knowledge about the SC regimen with the indication of nr-axSpA.

Question 6
Does the Agency agree that a single initial pediatric study plan (iPSP) for the iv formulation of secukinumab may be submitted with a full waiver for the indications of PsA and AS?

FDA Response
This approach appears reasonable. See PREA REQUIREMENTS below.

Discussion
No further discussion needed.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the

Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical

Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's handout is attached.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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