CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218436Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131325

MEETING PRELIMINARY COMMENTS

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

Attention: Patricia Duchene
Senior Global Program Regulatory Director

Dear Patricia Duchene:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for remibrutinib.

We also refer to your September 1, 2023, correspondence, received September 1, 2023, requesting a meeting to discuss the clinical data from the pivotal registration studies and the planned NDA submission of remibrutinib for the treatment of chronic spontaneous urticaria (CSU).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Phuong Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 1, 2023, 11:00 – 12:00 PM ET
Meeting Location: Videoconference

Application Number: IND 131325
Product Name: Remibrutinib
Indication: Chronic spontaneous urticaria
Sponsor Name: Novartis Pharmaceuticals Corporation

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 1, 2023, from 11:00 to 12:00 PM between Novartis and the Division of Pulmonology, Allergy, and Critical Care (DPACC). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1. BACKGROUND

Novartis submitted a pre-NDA meeting request dated September 1, 2023, and the Division granted the meeting on September 15, 2023. The purpose of the meeting is to discuss the clinical data from the pivotal registration studies and the planned NDA submission of remibrutinib for the treatment of chronic spontaneous urticaria. The Sponsor's questions from the briefing package submitted on September 25, 2023, are listed below in italics, followed by FDA's response in normal font.

2. QUESTIONS AND RESPONSES

Nonclinical

Question 1
Does the Agency agree that the proposed content of the non-clinical package is adequate to support the remibrutinib NDA?

FDA Response to Question 1
Yes, we agree.

Clinical

Question 2
Does the Agency agree that the proposed content of the clinical pharmacology package is adequate to support the remibrutinib NDA?

FDA Response to Question 2
Yes, we agree.

Question 3
Does the Agency agree that the remibrutinib clinical data package is adequate for the assessment of the safety and efficacy of remibrutinib 25 mg b.i.d. in the proposed CSU indication: "Remibrutinib (LOU064) is indicated for the treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1-antihistamine treatment"?

FDA Response to Question 3
Your initial NDA submission will include the following clinical trial data to support your proposed indication:

- Placebo-controlled efficacy and safety data from all subjects in the two pivotal trials CLOU064A2301 and CLOU064A2302 through Week 24, along with 52-week remibrutinib exposure data in 70 subjects from CLOU064A2301 and 56 subjects from CLOU064A2302 who have completed the trial

- Data from the week 24 interim analysis of the ongoing trial, CLOU064A1301, a phase 3, open-label study conducted in Japan

- Results from the completed phase 2 dose-ranging trial, CLOU064A2201, and the associated open label extension (OLE), CLOU064A2201E1

As conveyed in the Written Responses dated March 24, 2023, we strongly recommend including complete data from the 52-week pivotal trials at the time the NDA is submitted for filing and review. For a new molecular entity (NME) intended for the long-term treatment of a symptomatic disease, it will be important to have sufficient information to

support the benefit/risk assessment. Submission of the NDA prior to completion of the pivotal trials and with limited long-term safety data, entails risk if additional information is needed to inform the safety assessment during the review.

Question 4

a) *Does the Agency agree with the proposal for the submission of semi-automated enhanced narratives for patients in whom pregnancy was detected while being exposed to study treatment?*

FDA Response to Question 4a

Your proposal to provide semi-automated enhanced narratives for patients who become pregnant while exposed to study drug appears reasonable. However, we remind you that further details may be requested during the review if deemed necessary.

b) *Does the Agency agree with the selected definitions for the additional safety topics proposed by the Agency?*

FDA Response to Question 4b

In addition to the selected definitions for identifying adverse events of special interest (AESIs) of infections, cytopenias, and risk for bleeding, you have proposed to include safety analyses for arrhythmias, diarrhea, arthralgias, and hypertensions defined by the respective MedDRA SMQs and/or HLTs. These additional safety analyses appear reasonable.

Question 5

Does the Agency agree with the proposed content of the 120-Day Safety Update Report?

FDA Response to Question 5

The proposal to include the final CSRs and completed datasets from the two pivotal studies, CLOU064A2301 and CLOU064A2302, the phase 3 study conducted in Japan, CLOU064A1301, and the data collected in studies CLOU064A2303B (long-term safety), CLOU064A2305 (ABPM), CLOU064F12301 (pediatric in CSU), and CLOU064A2304 (3 arm study with omalizumab comparator), is acceptable. See also response to Question 3.

Question 6

Does the Agency agree that the proposed content of the submission dossier, as outlined in the electronic common technical document (eCTD) draft table of content, constitutes a complete application adequate for filing the NDA and permitting a substantive review?

FDA Response to Question 6

The proposed content as outlined in the eCTD draft table of content appears sufficient for filing purposes. However, we may request further details at the time of review. In

addition to comments provided in the Written Responses dated March 24, 2023, regarding the general content of your planned NDA submission, we refer you to FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*[1]

Question 7
Does the Agency intend to consult an external Advisory Committee as part of the review of the remibrutinib NDA for the treatment of CSU?

FDA Response to Question 7
Based on preliminary information available in the meeting package, we do not anticipate the need to convene the Pulmonary-Allergy Drugs Advisory Committee (PADAC) to discuss your NDA application for remibrutinib and the proposed CSU indication. However, a final determination will be made upon submission, filing, and review of your NDA. The FDA will promptly communicate if an Advisory Committee meeting is needed.

3. ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 15, 2023, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

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

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[3] https://www.fda.gov/media/86340/download
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[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

- 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.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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*

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-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*.[9]

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

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/

PHUONG N TON
10/27/2023 05:44:24 PM

IND 131325

MEETING MINUTES

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

Attention: Maria Pang, PhD
Senior Global Program Regulatory Manager, Regulatory Affairs

Dear Dr. Pang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for remibrutinib (LOU064).

We also refer to the telecon between representatives of your firm and the FDA on December 3, 2020. The purpose of the meeting was to discuss the proposed phase 3 studies for remibrutinib for the treatment of chronic spontaneous urticaria.

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 me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Phuong Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: December 3, 2020; 11:00 AM – 12:00 PM EST

Application Number: IND 131325
Product Name: Remibrutinib (LOU064)
Indication: Chronic spontaneous urticaria
Sponsor Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Sally Seymour, MD
Meeting Recorder: Nina Ton, PharmD

FDA ATTENDEES

Sally Seymour, MD, Division Director, Division of Pulmonology, Allergy, and Critical Care (DPACC), Office of Immunology and Inflammation (OII)
Banu Karimi-Shah, MD, Deputy Director, DPACC, OII
Stacy Chin, MD, Clinical Team Leader, DPACC, OII
Kelly Stone, MD, PhD, Acting Clinical Team Leader, DPACC, OII
Katherine Clarridge, MD, Clinical Reviewer, DPACC, OII
Jennifer Lan, MD, Clinical Reviewer, DPACC, OII
Yunzhao Ren, PhD, Acting Team Leader, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Carol Galvis, PhD, Pharmacology/Toxicology Team Leader, Division of Pharm/Tox for Immunology and Inflammation (DPT-II) , OII
Luqi Pei, PhD, Pharmacology/Toxicology Reviewer, DPT-II, OII
Yongman Kim, PhD, Acting Team Leader, Division of Biometrics III, Office of Biostatistics (OB)
Susan Duke, MS, MS, Biostatistics Reviewer, Division of Biometrics III, OB
Suyoung Tina Chang, MD, Reviewer, Good Clinical Practice Assessment Branch (GCPAB), Division Of Clinical Compliance Evaluation (DCCE), Office Of Scientific Investigations (OSI)
Jacqueline Sheppard, Team Leader, Division of Risk Management (DRM), Office of Surveillance and Epidemiology (OSE)
Carlisha Gentles, PharmD, Risk Management Analyst, DRM, OSE
Cristina Attinello, MPH, Safety Regulatory Project Manager, OSE
Nina Ton, PharmD, Senior Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation, Office of Regulatory Operations

SPONSOR ATTENDEES

Angelika Jahreis, Global Development Unit Head

Barbara Ambros, Global Program Head
Brian Porter, Clinical Development Head – Immunology
Sibylle Haemmerle, Global Program Clinical Head
Julian Storim, Sr. Clinical Development Medical Director
Olivier Chambenoit, US Clinical Development Franchise Head
Alis Burciu, Global Program Safety Lead
Ignacio Rodriguez, Global Head, Patient Safety
Peter End, Associate Director, PK Sciences
Bruno Cenni, Director, Translational Medicine
Bruno Bieth, Associate Director, Pharmacometrics
Karine Lheritier, Director, Biostatistics
Marc Vandemeulebroecke, Executive Director, Biostatistics
Gretchen Trout, Regulatory Policy & FDA Liaison
Paula Rinaldi, US Head Drug Regulatory Affairs Global
Penelope Giles, Global Development Unit Head, Regulatory
Ulrike Hornberger, Global Therapeutic Area Lead, Regulatory
Maria Pang, Sr. Global Program Regulatory Manager
Sebastiano Corridore, Global Program Regulatory Manager

1. BACKGROUND

Novartis submitted a Type B meeting request dated September 14, 2020, to discuss the proposed phase 3 studies for remibrutinib for the treatment of chronic spontaneous urticaria (CSU). The Division provided preliminary comments to the Sponsor's questions in the briefing package via electronic correspondence dated November 24, 2020. Novartis communicated to the Division via email dated December 1, 2020, that the Sponsor requested to focus the discussion on Questions 2a, 3a, 3b, 3c, 3d and 5. The Sponsor also provided a response document and the responses are incorporated under the corresponding FDA preliminary comments. The Sponsor's questions from the briefing package received October 15, 2020, and the responses are provided below in italics, the FDA's responses are in normal font, and the meeting discussion is in bold.

2. DISCUSSION

Nonclinical

Question 1
Novartis proposes the non-clinical program outlined is adequate to support the Phase 3 clinical program. Novartis also proposes the non-clinical program will be adequate for NDA. Does the Agency agree?

FDA Response to Question 1
We agree that your nonclinical program is adequate to support the phase 3 clinical trials of remibrutinib. Submit the reports of the planned peri- and post-natal developmental

(PPND) toxicity study and ongoing carcinogenicity studies in your NDA. A final decision of the adequacy of the nonclinical data will be made at a later time.

Meeting Discussion
This question was not discussed.

Clinical

Question 2a
Novartis proposes that the PK data of remibrutinib in different populations available to date are sufficient to start Phase 3, and that the plans to further characterize PK in subpopulations (organ impaired) during Phase 3 would be sufficient to support a NDA. Does the Agency agree?

FDA Response to Question 2a
We acknowledge that Novartis has adequately characterized the PK profile of remibrutinib in healthy subjects. We recommend that you sufficiently characterize the PK profile of remibrutinib in patients with CSU due to the non-linear PK properties and uncertainty of the BTK level difference between healthy subjects and patients with CSU.

We expect that the relative bioavailability Study X2105 also evaluates the food effect on the proposed tablet formulation, as the food effect must be evaluated for a to-be-marketed formulation intended for oral administration.

We acknowledge that Novartis plans to conduct a clinical study to evaluate remibrutinib PK in subjects with hepatic impairment. We recommend that you conduct a clinical study to evaluate remibrutinib PK in subjects with renal impairment when the updated results from the mass balance study (Study X2104) are available.

Novartis Response
We consider that data from the Phase 2 final dataset would adequately address the request and provide a full PK characterisation in CSU patients. Novartis will share the complete PK data set after final analysis. So far, there is no evidence for differences between healthy volunteers and CSU patients neither disease related expression nor as putative changes in expression due to treatment. Proposed doses (25mg and above) will fully neutralize BTK in blood and so small changes may not be relevant.
Novartis agrees to investigate the potential food effect with the to-be marketed formulation in a subsequent study separately.

Novartis is currently conducting a human ADME study. In line with animal data from four ADME studies in different species, renal excretion of drug related material is well below 30% of the total dose and the contribution of renal clearance to the overall clearance appears to be very low. Novartis would consider to waive a dedicated renal impairment study if mass balance in humans after oral and iv administration would finally confirm the low renal excretion in humans.

Meeting Discussion
Novartis discussed the response provided above and noted that the renal impairment study may not be needed when the results of the mass balance study are available. The FDA acknowledged the Sponsor's rationale and stated that the need to conduct the renal impairment study will depend on the results of the mass balance study.

Question 2b
Novartis proposes that the evaluation of the DDI potential of remibrutinib is adequate to initiate Phase 3 and that plans for further investigations are adequate for an NDA. Does the Agency agree?

FDA Response to Question 2b
Although your current in vitro and in vivo DDI-related clinical pharmacology results may support the initiation of phase 3 study with 25 mg BID regimen, we expect that a DDI clinical study between remibrutinib and a CYP3A4 strong inducer will be conducted in your clinical program. In addition, we note that the R values based on in vitro Ki and IC50 values of remibrutinib for certain transporters, including OATP1B1, are marginal for higher dose. Therefore, the need for clinical studies to evaluate the transporter-related DDIs will depend on the current ongoing in vitro investigations and the final proposed dose for the CSU clinical program.

Novartis Response
We agree with the suggestion from the Agency and will conduct a study with strong CYP3A4 inducers as well as transporters. In vitro investigations on transporters were concluded and did not change the overall results from previous studies or revealed new flags.

Meeting Discussion
The FDA asked if the sponsor is aware of the recent shortage of rifampin for the DDI study to evaluate the effect of CYP3A4 inducer. The Sponsor replied that they were not aware of this shortage. The FDA will provide recommendations for CYP3A4 inducer alternatives for use in DDI studies as post-meeting comments.

Post-Meeting Comments
The FDA has recently become aware of nitrosamine impurities above the acceptable limits in marketed rifampicin products and issued Drug Safety Statements (https://www.fda.gov/drugs/drug-safety-and-availability/fda-works-mitigate-shortages-rifampin-and-rifapentine-after-manufacturers-find-nitrosamine). As a result, the use of rifampicin products with a 1-methyl-4-nitrosopiperazine (MNP) impurity level above 0.16 ppm is not acceptable for healthy subjects and the proposed study should not be conducted. Based on the available information, the FDA recommends that carbamazepine be considered as an alternative to rifampin to investigate the impact of induction on the PK of a drug. A dosing regimen of 300 mg twice daily carbamazepine for a pre-treatment

period of 14 days is expected to reach its maximal CYP3A induction effect. It is recommended that carbamazepine dosing be initiated from a lower dose (e.g., at 100 mg BID and titrated in 100 mg increments to 300 mg BID over 3-7 days) to improve the tolerability. Alternatively, phenytoin can be considered as a secondary alternative to evaluate the impact of induction. The phenytoin dose is 300 mg/day (given as a once daily, twice a day, or three times a day dose) for a pre-treatment period of about 14 days. If you would like to propose other alternative approaches, please provide your justification.

Based on the limited data provided in the meeting package, the FDA has the following comments to consider when designing your CYP3A4 inducer DDI study for remibrutinib:

- **It appears that remibrutinib is extensively metabolized mainly by CYP3A. In addition, its limited bioavailability (~34%) indicates a substantial first-pass metabolism (mainly hepatic) and large clearance value, which makes it susceptible to significant DDI with CYP3A modulators. Therefore, it is very likely that remibrutinib is subject to a large induction effect with a strong CYP3A inducer such as rifampin.**

- **Thus, we recommend that you conduct a DDI study with a moderate CYP3A inducer (e.g., efavirenz or another drug) first. Pending results from this study and the dose/exposure-efficacy relationship of remibrutinib, it may be possible to derive labeling recommendations for strong CYP3A inducers based on results from the moderate CYP3A inducer study. Simulation from a PBPK model may also be potentially used to provide supportive evidence.**

Question 2c

Novartis proposes that the characterization of human metabolites, their safety and overall disposition pathways of remibrutinib across species completed to date are adequate to support the initiation of Phase 3 and that the plans for further investigations are adequate to support an NDA for remibrutinib. Does the Agency agree?

FDA Response to Question 2c

We agree that human metabolites data collected to date are adequate to support the initiation of phase 3 clinical trials of remibrutinib. We also agree with your plan for further investigation of metabolic profiles of remibrutinib in humans. We defer the determination of the adequacy of data to support an NDA for remibrutinib when the data are submitted and reviewed.

Novartis Response

Metabolite data have already been evaluated across species from safety studies as well as after multiple doses in a human volunteer study indicating that all of the circulating

metabolites in humans are also detected in rat or dog. We currently verify those results against data obtained from the human ADME study.

Meeting Discussion
This question was not discussed.

Question 2d
Novartis proposes that the current assessment of cardiac safety (QTc) of remibrutinib is adequate to enter into Phase 3 and to apply for a TQT study waiver. Does the Agency agree?

FDA Response to Question 2d
Based on the information provided, the proposed studies (CLOU064X2101 and CLOU064X1101) appear adequate to characterize the potential for your drug to prolong the QTc per ICH E14 Q&A 5.1. Whether these data exclude a 10-ms mean QTc effect at the highest clinically relevant exposure will be a review issue when the data are submitted. Additionally, we have the following comments for you to consider:

a. We are also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

b. When you submit your QT evaluation report, include a completed version of the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinaryreview-team-cardiac-safety-studies-formerly-qt-irt).

Novartis Response
Novartis will provide further detailed data on cardiac safety separately with a justification to waive a TQT study.

Meeting Discussion
This question was not discussed.

Question 3
Does the Agency agree with the proposed design of the Phase 3 studies (CLOU064A2301 and CLOU064A2302), specifically:

a. That the design of the Phase 3 studies is adequate to assess efficacy and safety?
b. That the proposed inclusion/exclusion criteria in the Phase 3 studies will yield a subject population that will support the proposed indication?
c. With the proposed primary and key secondary objectives and endpoints?
d. With the proposed estimand strategy for Phase 3?

e. *With the statistical analysis methods for Phase 3?*

FDA Response to Question 3

While you have requested an End of Phase 2 meeting to discuss your CSU clinical development program for remibrutinib, the only data available in CSU patients is from your ongoing phase 2 study CLOU064A2201, which is approximately 50% complete. As such, we believe it is premature to discuss your phase 3 program given the limited amount of efficacy and safety data provided in the meeting package.

Remibrutinib is an unapproved, new molecular entity (NME) that is expected to carry similar risks and toxicities as other members of the BTK inhibitor class of drugs. Given the availability of alternative therapies for CSU, your development program will need to clearly demonstrate that remibrutinib has a favorable benefit/risk assessment for this indication. Because of the known risks of BTK inhibitors and lack of extensive safety information with remibrutinib itself, you will need to provide a more robust safety database than what you have proposed. This will also entail identifying a target population most likely to benefit from remibrutinib treatment to offset the potential risks.

In light of your incomplete phase 2 program and with these overarching concepts in mind, we have provided the following high-level responses to your questions. Please note, our advice may change once you have completed your phase 2 studies and more data becomes available.

a. *Adequacy of Phase 3 study design:* No, we do not agree that the design of your phase 3 trials is adequate to assess efficacy and safety of remibrutinib for treatment of CSU. As mentioned above, your proposed safety database is inadequate to support the benefit/risk assessment. Furthermore, for a chronically administered drug in a new therapeutic class for this indication, it is important to assess for the durability of the treatment response. You will need to conduct two adequate and well-controlled trials of 52- and 24-weeks duration, respectively, with the control arm extending throughout the entire treatment period. While you have proposed trials of 52 and 24-weeks duration, your proposed study designs call for open label treatment after week 12 with no comparator. Given the limitations of interpreting uncontrolled open-label data, your proposed study design would not provide sufficient evidence to determine safety or efficacy of your product. In addition, we recommend pre-specifying adverse events of special interest (AESI) based on the known safety profile of BTK inhibitors (e.g., infection, bleeding, cytopenias).

Meeting Discussion

Novartis acknowledged that only partial phase 2 data are currently available, but find the preliminary efficacy and safety data promising and consider the data sufficient to inform dose selection and the target population. The Sponsor clarified that phase 2 data will be fully available, analyzed and incorporated into the development plan as needed prior to the initiation of the phase 3 trials. The

Sponsor alluded to the difficulty of maintaining a placebo control arm for an entire year in the phase 3 clinical trial given the availability of other therapies and potential for drop-outs and missing data. As an alternative design, the Sponsor proposed to conduct 12-week double-blinded, placebo-controlled trials with re-randomization of the placebo arm to one of two doses of remibrutinib (i.e., 25 mg BID and a lower dose) after week 12. The FDA maintained that a longer duration of placebo controlled data is necessary to inform the safety and efficacy of remibrutinib for CSU, particularly since remibrutinib is a new molecular entity intended for chronic use > 12 weeks. Novartis stressed the difficulty in maintaining patients on placebo for 52 weeks. However, the FDA reminded the Sponsor that all subjects should continue to receive background standard of care and that interpretation of safety data is severely limited in the absence of a placebo control arm. In response, Novartis proposed to extend the placebo arm to 24 weeks for both phase 3 trials. The FDA considered this proposal acceptable and planned to provide further comments post meeting regarding the proposal to re-randomize placebo patients after 24 weeks to receive either 25 mg BID or a lower dose.

Post-Meeting Comments

Your plan for a 24-week double blind, placebo-controlled treatment period in both phase 3 trials appears reasonable; however, additional data may be required if new safety signals emerge. Re-randomizing patients in the placebo arm to receive remibrutinib (either 25 mg BID or a lower dose) after Week 24 is at your discretion. However, you should consider what additional information you hope to obtain from re-randomization and whether re-randomization to a lower dose will provide adequate long-term safety data for the remibrutinib dose you intend to propose for labeling.

b. *Proposed inclusion/exclusion criteria:* Your proposed eligibility criteria would enroll patients who remain symptomatic despite treatment with locally approved doses of second generation H1-antihistamines. Current treatment guidelines recommend up to 4x approved dosages of second generation H1-antihistamines followed by anti-IgE therapy with omalizumab as second and third line therapies, respectively. As noted above, it is critical to identify and study the target population most likely to benefit from remibrutinib treatment given the context of available therapies and potential risks associated with BTK inhibitors. At a minimum, your phase 3 trials should enroll patients who have failed to respond to higher than approved doses of H1-antihistamines. However, we also recommend that you consider evaluating a study population who have failed anti-IgE treatment to capture a truly refractory population with unmet need.

Meeting Discussion

Novartis clarified that the intended population for remibrutinib include all pre-biologic CSU patients (i.e., those with inadequate response to higher doses of H1-antihistamines, based on local guidelines, who have not initiated biologic

therapy) as well as those refractory to anti-IgE. However, the study will stratify randomization by prior biologic use for CSU. The FDA reiterated the importance of clearly defining the target population and focusing on patients who are refractory to higher than approved doses of antihistamines. Given that antihistamines at approved and up to 4x approved doses are first and second line treatments, respectively, for CSU, we expect the target population to reflect patients who are likely to receive a BTK inhibitor based on the current U.S. treatment guidelines. In response, the Sponsor stated that higher than approved dosages of antihistamines are not geographically standardized across countries and further mentioned individual intolerance to high doses due to the side effect profile. For this reason, the Sponsor envisions positioning remibrutinib therapy between antihistamines and omalizumab, with some having failed higher doses of antihistamines but not all, due to the advantages of an oral route of administration. The FDA acknowledged that some patients are unable to tolerate high-dose antihistamines, but noted that the convenience of an orally administered drug may not be sufficient to overcome the potential risks of a BTK inhibitor in the context of available therapies with extensive clinical safety experience. It is therefore in the Sponsor's best interest to identify and study a target CSU population for whom the potential benefits will outweigh the potential risks.

c. *Proposed primary and key secondary objectives and endpoints:* You propose to use change from baseline in weekly UAS7 score at Week 12 as your primary endpoint for both trials. While we recognize the value of UAS7 as a meaningful outcome measure for CSU, we recommend using the individual components of the UAS7 (Itch Severity Score and Hive Severity Score) as co-primary endpoints, rather than total UAS7 as a single primary endpoint. Designating Itch Severity Score (ISS7) and Hive Severity Score (HSS7) as co-primary endpoints will ensure that efficacy is not driven by a single component. With regard to the timing of the primary endpoint analysis, we agree that Week 12 is acceptable; however, as stated in the response above, you should continue to collect efficacy data at later timepoints in the controlled trials to demonstrate the durability of response.

   We do not have sufficient support regarding the content validity of the DLQI in order to deem it suitable for informing regulatory decision making (b) (4) The DLQI contains questions that ask about various concepts related to a skin problem and its treatment, which may lack clinical relevance and may be insensitive in detecting potential treatment effects in your patient population. Further, there are issues with the inclusion of multi-barreled questions (questions measuring more than one concept, e.g., one item asks how "itchy, sore, painful or stinging" the skin has been; another item asks about the skin's interference with "going shopping or looking after [one's] home or garden") which can lead to unwanted variability in the data. If you are interested in assessment of CSU-related impacts, we encourage you to use a more disease

specific instrument that evaluates the impacts of CSU symptoms on patients' daily lives in order to provide meaningful information regarding the clinical benefit of your treatment.

Meeting Discussion

Acknowledging the FDA's comments, Novartis requested to maintain UAS7 as the primary endpoint in order to accommodate the global nature of the trial and all regulatory authorities under which they intend to seek registration. While UAS7 has been assessed in other CSU development programs, the FDA's main concern with its use as the primary efficacy endpoint is the possibility that a reduction in hive count may drive the results in the absence of improvement in itch. As both itch and hive component scores of the UAS7 are considered clinically important to the overall treatment effect, the FDA continued to recommend using ISS7 and HSS7 as co-primary endpoints. The Sponsor expressed concern that other regions such as Europe and Japan may not accept a co-primary endpoint. Although the Sponsor has not specifically inquired about acceptability of HSS7 and ISS7 as co-primary endpoints, they are confident that UAS7 is widely accepted as a primary endpoint for CSU. The Sponsor offered the possibility of designating different primary endpoints in the protocol along with having separate statistical analysis plans for the U.S. and rest of the world. While this proposal is acceptable and has been done for other non-CSU development programs, the FDA acknowledged the Sponsor's feedback. The FDA stated it will reach out to EMA and PMDA to discuss recommendations for CSU programs.

d. *Proposed estimand strategy:* Hypothetical strategy is not appropriate because the hypothetical scenario of non-availability of the rescue medication may not reflect real world clinical practice and be problematic in answering the scientific question of interest. However, we do agree with your handling of treatment interruption/incompliance after Week 8 due to other non-human controlled emergency situations (e.g. COVID-19) using a hypothetical estimand strategy as described above because these intercurrent events are likely to be due to random chance.

   It is unclear whether you have chosen to prohibit the use of systemic corticosteroids during the study due to concern for infection or interference with interpretation of efficacy. Rescue medications, including oral corticosteroids, should be permitted as standard of care. In the event a subject requires rescue medication, this would be considered a treatment failure. As such, assign the value from the time of rescue medication administration to Week 12 to the worst possible score for the recommended co-primary endpoints.

Novartis response

We would like to clarify that rescue medication does not include oral corticosteroids. As defined in the synopsis of the Phase 3 study (section 6.2.3 Rescue medication), second generation H1-antihistamines are allowed as rescue medication, used on an as needed

basis for subjects with flare-ups of unbearable symptoms of their disease during screening, treatment and follow-up periods. A change of the rescue medication for an individual subject is not permitted unless in case of adverse reactions attributable to the current prescribed rescue medication.

Moreover, the choice to prohibit the use of systemic corticosteroids during the study is due to concern of interference with the interpretation of efficacy. Especially, it is considered that use of systemic corticosteroid very close to the primary efficacy assessment (e.g. after Week 8) is an intercurrent event which might confound the interpretation of the primary Estimand. To ensure the wellbeing of the patient, oral corticosteroids are allowed if used for short interventions after the primary endpoint was achieved at Week 12. For intake of biologic treatment, it is expected to be very few or even none. So the scientific question of clinical interest was defined as if the patients had not used these prohibited medications.

With respect to rescue medication as described in the protocol (H1-antihistamines), treatment policy strategy is used to handle the intercurrent event of the use of rescue therapy. If the Agency considers that the hypothetical strategy is not appropriate for the intercurrent event of intake of strongly confounding prohibited medication (e.g. biologics treatment at any time before Week 12, cyclosporine after Week 8, systemic corticosteroids after Week 8), Novartis then proposes the treatment policy strategy for this intercurrent event as the primary Estimand. Novartis would also apply the composite strategy in the supplementary analysis, where we consider unfavorable clinical outcome as a change from baseline in UAS7 score is 0 (no clinical improvement from baseline at all), rather than the worst possible score for the primary endpoint at Week 12.

Meeting Discussion

The FDA acknowledged the Sponsor's response but strongly recommended the composite strategy using the worst possible score when rescue medications are taken to indicate treatment failure, which is in alignment with ICH E9(R1). Referring to experience in a different indication, the FDA noted that accounting for treatment failures via composite variable strategy provides a more real-world quantification of the treatment failures and is expected to occur at a higher frequency in the placebo arm (assuming the active arm is sufficiently efficacious).

Post-Meeting Comments

See also ICH E9(R1) page 15:

> **A composite variable strategy can avoid statistical assumptions about data after an intercurrent event by considering occurrence of the intercurrent event as a component of the outcome. The potential concern relates less to assumptions for estimation, and more to the interpretation of the estimated treatment effect. For the estimand to be interpretable, if scores are assigned for failure because the intercurrent event occurs, these should meaningfully reflect the lack of benefit to the patient (e.g. death**

may be reflected differently than discontinuation of treatment due to adverse event).

There is additional information under the estimand strategies section for composite variable strategy on page 8. We also note that a Novartis statistician co-authored this guidance.

e. *Statistical analysis methods:* As you plan to use MMRM as your confirmatory analysis method, it will be important to include a contrast such that the question being answered in the analysis is at the landmark timepoint of Week 12, rather than the average over repeated measures across the span of timepoints of the study. This aligns with the estimand strategy recommended above.

Meeting Discussion
This topic was not discussed.

Additional Statistical Comments
We have the following general comments regarding statistical issues you may consider when designing your phase 3 development program. For your safety assessment, you have described your plans for descriptive statistics on your safety evaluation of adverse events, vital signs, 12-lead ECG and clinical laboratory evaluations. To ensure a reliable safety evaluation and to support the benefit-risk assessment, we recommend you submit the following:

1. A discussion of the sufficiency of the sample size and duration of studies in the development program to reliably evaluate safety. In particular, for your adverse events of special interest (AESIs), consider in your safety planning the sufficiency of the sample size to reliably evaluate safety. Also consider your method of data collection, including whether each outcome will be ascertained based on specific items in a structured checklist/questionnaire (active ascertainment) or based on a planned grouping of specific PTs mapped from voluntary participant responses to open-ended questions (passive ascertainment).

2. A plan for defining identified safety outcomes, including any planned groupings of AEs, e.g., with Standardized MedDRA Queries (SMQs) or preferred terms (PTs) or System Organ Classes (SOCs) or some other grouping of multiple events/PTs representing the same or similar underlying concepts.

3. A plan for analyzing adverse events, both within studies and integrated across studies.

4. Appropriately account for study differences in integrated analyses to avoid confounding by study (e.g., Simpson's Paradox ,), either by adjusting for or stratifying by study. The method/weights to be used for stratification should be specified in the integrated summary of safety (ISS) SAP.

5. At a minimum, include by-treatment comparisons for adverse events (AEs) leading to discontinuation, deaths, SAEs, adverse events of special interest and most frequent adverse events occurring in greater frequency in test subjects.

6. For serious adverse events (SAEs) and AESIs, we recommend prospectively planned analyses that compare treatment groups with respect to risk, e.g., with a rate ratio, risk difference, hazard ratio, or relative risk, along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison (no hypothesis testing is necessary) and justify your reasoning for the risk comparison method chosen (i.e., risk difference is generally preferred but there may be scenarios where another method better describes patient risk).

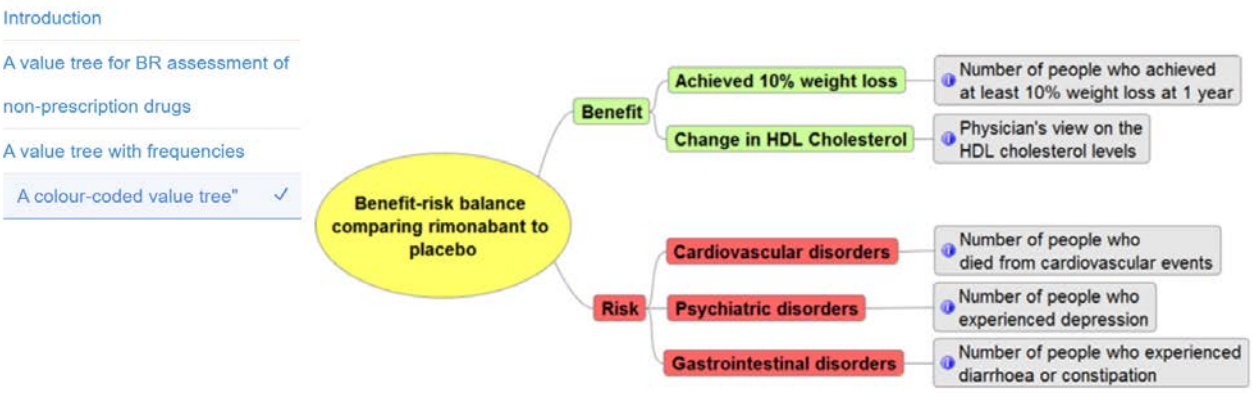
7. Include in your ISS SAP your plan for AESIs. Provide raw cumulative incidence proportions, and if there are differing follow-up times, provide exposure-adjusted incidence rates to account for the differing follow-up times between treatment arms. Exposure time calculations should be carefully defined in your ISS SAP—exposure time should generally include the time to the occurrence of the event in patients who had an event, or the time to the end of follow-up in patients who did not have an event, with a careful definition of “follow-up.”

   Post-Meeting Comment
   Note that if there are differing follow-up times between treatment arms then exposure-adjusted incidence rates will be needed.

8. A plan for communicating results for key benefit and risk outcomes. We encourage you to consider presenting visual displays. For key risk outcomes, you can consider graphical approaches such as those located at the following website https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome

   For example, you might consider an adverse event plot with frequency and risk differences plotted together for the most common adverse events and a shift plot for laboratory evaluations.

9. Identification of key potential benefits and risks, e.g., in a value tree (example value tree is below).



Meeting Discussion

This topic was not discussed.

Additional Clinical Outcome Assessment (COA) Comments

1. Submit exact copies of all clinical outcome assessments intended to support prespecified alpha-controlled endpoints (i.e., ISS7, HSS7, UAS7, AAS7, UCT, DLQI) as you plan to administer them in the proposed phase 3 clinical trials (e.g., electronic diary screenshots) for Agency review and comment.

2. Ensure that the Urticaria Activity Score-7 (UAS7) includes specific instructions for patients. We strongly recommend including specific instructions and clearly defining the recall period (e.g., over the past 24 hours) to minimize variability in patients' responses.

3. For PRO assessments, we recommend use of patient-friendly terminology (e.g., "hives" and "itch" rather than "wheals" and "pruritis") to maximize comprehensibility of the instrument across patients of varying health literacy levels. Choice of proper terminology may be guided by the results of cognitive interviews in patients who represent your target patient population.

4. We recommend that you explore inclusion of multiple anchor scales for exploratory purposes to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change in your primary endpoint assessment from the patient perspective. The anchor scales should be administered at comparable time points as, but completed after, the primary endpoint assessment (e.g., if the primary endpoint is calculated as a weekly score, then you may consider administering anchor scales weekly). We recommend that you include at least the following anchor scales to generate a threshold for improvement that represents a meaningful amount of change in your target population:

    a. Static, current state patient global impression of severity (PGIS) scale

    b. Patient global impression of change (PGIC) scale

(Note: In contrast to the PGIC scale, the PGIS scale is not subject to recall error and can also be used to assess change from baseline data. The PGIS scale is the preferred anchor scale over the PGIC scale; however, there is no perfect anchor scale and it is helpful to include multiple anchor scales for anchor-based analyses.)

Examples of PGIS and PGIC scales are as follows:

Example of a PGIS Scale:
Please choose the response below that best describes the severity of your <SYMPTOM/OVERALL STATUS/ETC.> over the past *(specify the appropriate recall period here)*.

□ None
□ Mild
□ Moderate
□ Severe

Example of a PGIC Scale:
Please choose the response below that best describes the overall change in your <SYMPTOM/OVERALL STATUS/ETC.> since you started taking the study medication.

□ Much better
□ A little better
□ No change
□ A little worse
□ Much worse

5. We recommend electronic data capture using a device with a reminder or alarm function, when appropriate and feasible, as this tends to facilitate operation, minimize the extent of missing data, and allows for the collection of other important information (e.g., timestamps for data input). You may refer to the FDA guidance for industry on electronic source data (see Guidance for Industry: *Electronic Source Data in Clinical Investigations*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-source-data-clinical-investigations).

   If you proceed with electronic data capture, we recommend that you perform usability testing of the selected devices with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the patient population. This would minimize the likelihood of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device. We also recommend that you implement a back-up plan prior to using the devices in your clinical trials, in case of any electronic device malfunctions.

Meeting Discussion
This topic was not discussed.

Question 4
Novartis proposes remibrutinib 25 mg b.i.d. for the planned Phase 3 pivotal clinical studies. Does the Agency agree?

FDA Response to Question 4
We are unable to agree or disagree with your proposal to carry forward the 25 mg BID dose into phase 3 trials given that preliminary efficacy data from phase 2 study CLOU064A2201 did not reveal dose ordering or a clear dose response. While it is at your discretion to evaluate a single dose/dosing regimen in Phase 3, this decision will entail some regulatory risk, particularly if significant safety issues are identified in your late phase program. Given the remibrutinib 10 mg BID dose appeared to produce similar effects in the interim analysis data provided in the meeting package, consider evaluating both the 10 mg and 25 mg BID doses in your phase 3 trials.

Meeting Discussion
This question was not discussed.

Question 5
Novartis considers that the safety and efficacy data available to date are adequate to support the start of the Phase 3 clinical program and that the planned Phase 3 development plan is sufficient to provide substantial evidence of safety and efficacy to support the NDA of remibrutinib for the treatment of subjects with CSU. Does the Agency agree?

FDA Response to Question 5
No, we do not agree. We strongly recommend completing your phase 2 program prior to initiating phase 3 trials. As currently designed, your phase 3 development program will not be sufficient to provide substantial evidence of safety and efficacy to support an NDA submission of remibrutinib for the treatment of subjects with CSU (see response to Question 3).

Meeting Discussion
Novartis commented that the expected patient exposure at the time of the primary analysis of 850 patients treated for 6 months and 350 patients treated for 1 year, meets ICH guidelines and safety requirements. The Sponsor inquired as to whether the phase 3 program would be sufficient to provide safety and efficacy data to support an NDA. The FDA noted that it is premature to comment on the size of the safety database without the benefit of reviewing the phase 2 data. The FDA further emphasized the importance of clearly defining adverse events of special interest (AESIs) and how this information will be presented to the FDA. The Sponsor agreed to use risk difference and its 95% confidence interval to address sufficiency of sample size in SAEs and AESIs. The FDA encourages this

for common AEs as well, and recommends graphical display of most common AE frequencies and risk differences together.[1] Note that if there are differing follow-up times between treatment arms that exposure-adjusted incidence rates will be needed, as described above in Additional Statistical Comments.

3. 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*.[2] 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.[3]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in

[1] See CTSPedia recommendation for most frequent on-therapy AE sorted by risk difference: https://www.ctspedia.org/do/view/CTSpedia/ClinAEGraph000

[2] 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.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are 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[5] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 FDA Study Data Technical 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,

[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. 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 FDA.gov.[6]

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

[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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[7] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[8]

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

[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/media/109533/download

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*.[9]

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

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

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* for more information.

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

4. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5. ACTION ITEMS

There were no action items.

6. ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting summary.

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/

PHUONG N TON
12/23/2020 05:38:10 PM