CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218276Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 134655

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Shivani Shah, PharmD, MBA
Senior Global Regulatory Manager
Regulatory Affairs
One Health Plaza, Building 337
East Hanover, New Jersey 07936-1080

Dear Dr. Shah:

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

We also refer to the teleconference between representatives of your firm and the FDA on December 14, 2022. The purpose of the meeting was to discuss the top-line data from the phase 3 study CLNP023C12302 (APPLY-PNH).

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

If you have any questions, contact Courtney Hamilton, Regulatory Project Manager at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Carrie Diamond, MD
Clinical Team Leader
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: December 14, 2022; 2:00-3:00 PM (ET)
Meeting Location: Teleconference

Application Number: IND 134655
Product Name: iptacopan

Indication: Treatment of paroxysmal nocturnal hemoglobinuria (PNH)
Sponsor Name: Novartis Pharmaceuticals
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Carrie Diamond, MD
Meeting Recorder: Courtney Hamilton, PharmD

FDA ATTENDEES

OCHEN, Division of Nonmalignant Hematology (DNH)
Ann Farrell, MD, Director
Rosanna Setse, MD, MPH, PhD, Deputy Director for Safety
Qin Ryan, MD, PhD Medical Officer, Safety
Carrie Diamond, MD, Clinical Team Lead
Donna Whyte-Stewart, MD, Clinical Reviewer

Office of Biostatistics (OB), Division of Biometrics IX
Yeh-Fong Chen, PhD, Statistical Team Lead
Huan Wang, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)
Doanh Tran, PhD, Clinical Pharmacology Team Lead
Li Wang, PhD, Clinical Pharmacology Reviewer

Office of Regulatory Operations (ORO)
Courtney Hamilton, PharmD, BCPS, Senior Regulatory Project Manager
Bijal Patel, Regulatory Project Manager

Office of New Drug Products (ONDP)
Theodore Carver, PhD, Senior Pharmaceutical Quality Assessor

SPONSOR ATTENDEES

Thomas Holbro, Global Program Head

Marion Dahlke, Global Program Clinical Head
Cécile Kerloëguen, Senior Clinical Development Director
Philippe Ferber, Senior Clinical Development Director
Rafael Levitch, Associate Clinical Development Director
Ronny Renfurm, Clinical Development Head Cardiovascular, Renal, Metabolism
Marty Lefkowitz, Clinical Development Head Cardiovascular, Renal, Metabolism
David Soergel, Cardio-Metabolic Development Unit Head
Susan Longman, Global Head Regulatory Affairs
Patricia Kay-Mugford, Regulatory Affairs Head Cardiovascular, Renal, Metabolism

Bhavini Patel, Global Regulatory Affairs, Senior Director
Paula Rinaldi, US Regulatory Affairs Head
Gautier Sala, Global Regulatory Affairs Therapeutic Area Load
Johanna Heinzerling, Global Regulatory Affairs Director
Shivani Shah, Global Regulatory Affairs Senior Manager
Gretchen Trout, Head, North America Policy, Regulatory Affairs
Nicolas Rouyrre, Global Program Biostatistics Head
Melanie Wright, Executive Director Biostatistics
Samopriyo Maitra, Director, Biostatistics
Ekkehard Glimm, Senior Director, Statistics
Markus Hinder, Global Program Safety Lead
Christine Thorburn, Global Program Safety Lead
Jincy Paulose, Executive Medical Director, US Medical Affairs
Antonio Risitano, MD, PhD, President of the International PNH Interest Group and Head of the Hematology and Hematopoietic Transplant Unit

1.0 BACKGROUND

Iptacopan is an oral, small molecule and selective inhibitor of complement factor B (FB). Iptacopan inhibits FB in the context of the C3 convertase, blocking alternative pathway (AP)-dependent C3 activation and the amplification loop of the classical and lectin pathway. Novartis is developing iptacopan for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Iptacopan was granted Breakthrough Therapy Designation for PNH and has Orphan Designation for PNH. Iptacopan is also being developed for other complement mediated hematologic and renal diseases.

Novartis has requested this Type B, Pre-NDA meeting to discuss top-line data from the pivotal phase 3 study CLNP023C12302 (APPLY-PNH).

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Novartis Pharmaceuticals, Inc. and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 505(b)(1) of the Food, Drug, and Cosmetics Act.

FDA sent Preliminary Comments to Novartis Pharmaceuticals on December 13, 2022.

2.0 DISCUSSION

2.1. Questions and Responses

Question 1: What is the Agency's view of the primary efficacy results from APPLY-PNH, which demonstrated the superiority of iptacopan 200 mg b.i.d. compared to anti-C5 therapy on hematological response endpoints, as evidence of clinically meaningful efficacy?

FDA Response: Study APPLY-PNH is a randomized (8:5), open-label study which enrolled 97 adults with PNH with residual anemia (hemoglobin (Hb) <10 g/dL) despite receiving a stable regimen of anti-C5 antibody therapy (eculizumab or ravulizumab) for at least 6 months prior to randomization. Subjects had a baseline Hb of 8.9 g/dL, and 58% received at least one transfusion in the previous 6 months prior to enrollment. Subjects were randomized to iptacopan monotherapy 200 mg twice a day (n=62) or to continue their anti-C5 regimen (n=35) for 24 weeks. There were two primary endpoints, an increase in Hb of ≥2 g/dL from baseline and Hb ≥12 g/dL, both in the absence of red blood cell (RBC) transfusions.

In the iptacopan arm, 51/62 (82%) subjects had a ≥2 g/dL increase in Hb from baseline, and 42/62 (68%) had a Hb ≥12 g/dL, both in the absence of RBC transfusions (p-value <0.0001). No subject in the anti-C5 inhibitor arm met the primary endpoints.

The primary efficacy results presented in this meeting package appear sufficient to support filing and review of the NDA. The decision of whether the efficacy results for the APPLY-PNH study support approval will be determined during the review of the NDA. We will conduct our own independent analysis of the datasets submitted in the application to confirm the efficacy claims. Please note, demonstration of durability of response will be an important review issue.

We have the following requests for clarification:

In your final statistical analysis plan (SAP) submitted on October 19, 2022, (SDN 70), you proposed to use the permutation test with conditional logistic regression model to test for the two primary endpoints of the response defined as having an increase from baseline in Hb ≥2 g/dL and the response defined as having Hb ≥12 g/dL. The primary and key secondary endpoints were planned to be tested using sequentially rejective graphical procedures, which is to first test the two primary endpoints with equal weights, and then subsequently test key secondary endpoints following the pre-defined weights and sequence for multiplicity adjustment. Please provide the rationale of using the permutation test for the two primary endpoints and clarify whether your results of the primary endpoints in Table 3-5 in the briefing book are based on the permutation test or not.

In addition, the footnote of Table 3-5 indicates that the results of the primary endpoints are based on the logistic regression model using Firth correction instead of the conditional logistic regression model. In the briefing book, you stated that "in order to address the convergence issues related to the possible presence of zero responders in a treatment arm or in a stratum, a Firth correction was applied to the logistic regression." Please confirm that you indeed encounter convergence issues when analyzing the primary efficacy endpoint and provide your analysis results based on the conditional logistic model and permutation test.

Meeting Discussion: The Agency clarified that the durability of response is an important consideration because PNH is a chronic disease, therefore, it is critical to have a good understanding of the long-term efficacy of the drug, beyond 168 days. The Agency recommended that the Sponsor include data showing durability of the drug with long-term exposure in patients.

The Agency further inquired about the number of patients that have been treated with iptacopan for more than a year. The Sponsor highlighted the following:

- **19 patients were treated with monotherapy for at least a year**
- **30 patients for at least 48 weeks**

The Sponsor clarified that the results for the primary endpoints shown in Tables 3-1 and 3-5 of the briefing book are based on permutation tests as specified in the study protocol. They also confirmed that they encountered the non-convergence issue with the pre-specified conditional logistic regression model because zero responder happened in the anti-C5 antibody group. The Agency provided the following comments regarding the analyses for major efficacy endpoints:

- **The Sponsor has included two stratification factors (anti-C5 antibody treatment and previous transfusion status) and three covariates (sex, age, and baseline hemoglobin) in addition to the treatment variable in the final analysis models. However, some of these covariates may not be needed or even problematic to be included. In particular, the Sponsor included an indicator variable of baseline hemoglobin ≥ 9 g/dL in their models when there is already an inclusion criterion of hemoglobin <10 g/dL. In addition, it is not clear which cutoff values the Sponsor should use for the covariates of baseline hemoglobin and age. Therefore, the Agency recommended the Sponsor perform re-analyses for all major efficacy endpoints without including these two covariates.**

- **For all binary endpoints, in the "safe to proceed" letter dated September 28, 2020, the Agency recommended that the primary analysis be based on the stratified Cochran–Mantel–Haenszel (CMH) test. Therefore, the Agency will determine the drug efficacy mainly based on the primary analysis of**

CMH. The Agency also recommended the Sponsor provide the estimate and 95% CI for the response rate difference for binary endpoints rather than the estimate and 95% CI for the odds ratio. The Sponsor's analyses based on the logistic regression with Firth correction can be used as a secondary analysis.

Regarding the permutation test, the Sponsor explained that the rationale of using the permutation test is that "the permutation test can improve the performance of conditional logistic regression, while still controlling the type I error rate". Considering that 1) the conditional logistic regression model had failed to converge and 2) the Sponsor has already used a graphic approach with pre-specified weight to control the type I error, the Agency asked the Sponsor to explain why the permutation test is needed and re-emphasized that the drug efficacy should be mainly based on the primary analysis of CMH. In addition, the Agency asked the Sponsor to provide their rationale for the pre-specified weights for all endpoints included in the graphic approach for multiplicity adjustment.

The Sponsor acknowledged the Agency's comments and recommendations. They agreed to provide the requested information in writing and will conduct the recommended analyses in the NDA submission.

Question 2: Does the Agency agree that the secondary efficacy results from APPLY-PNH (transfusion avoidance, change from baseline in Hb, absolute reticulocyte count, fatigue FACIT-F score and rate of clinical BTH) provide further relevant evidence of effectiveness of iptacopan across a spectrum of clinically meaningful endpoints for PNH and, together with the primary endpoints, are adequate to support registration?

FDA Response: In the meeting package, you report the key secondary efficacy results from APPLY-PNH which include transfusion avoidance, change in baseline Hb, absolute reticulocyte count, FACIT-F score, and clinical breakthrough hemolysis, were all statistically significant. In total, 60/62 (97%) subjects in the iptacopan arm were transfusion avoidant compared to 14/35 (40%) in the anti-C5 arm (p-value <0.001). In addition, the mean change from baseline in Hb was 3.6 g/dL for the iptacopan arm and -0.04 g/dL for the anti-C5 arm, change from baseline in absolute reticulocyte count was -115.9 x 10^9/L for the iptacopan arm and 0.37x10^9/L for the anti-C5 arm, and change in FACIT-F score was 8.6 in the iptacopan arm and 0.3 in the anti-C5 arm (p-value <0.0001). The proportion of subjects with clinical breakthrough hemolysis in the iptacopan arm was 2/62 (3.2%) compared to 6/35 (17%) in the anti-C5 complement arm (p-value = 0.0118). Key secondary endpoints of lactate dehydrogenase (LDH) and major adverse vascular events (MAVE) were not statistically significant.

The efficacy results presented in this meeting package appear sufficient to support filing and review of the NDA. The decision of whether the results of the secondary endpoints are adequate to support approval, will be determined during

the review of the NDA. Please note, as the trial design is open-label, the results of the FACIT-F will be difficult to interpret.

We have the following requests for additional information:

In your final SAP submitted on October 19, 2022, (SDN 70), you stated that the following change was made on October 12, 2022: "the zero inflated models specified in previous versions of SAP lead to convergence issues and hence switching to protocol specified negative binomial model." In the previous version of the SAP issued on October 28, 2021, a backup plan by considering only treatment as a factor in the zero-inflated model for dealing with the convergence issue was already specified. Clarify why in the final version of the SAP issued on October 12, 2022, you specified a different model, i.e., negative binomial model, to deal with the convergence issue.

Provide the database lock date for trial APPLY-PNH.

Meeting Discussion: The Sponsor stated that the zero-inflated models specified in the previous versions of SAP was abandoned because it led to convergence issues at time of dry run. However, the Agency asked the Sponsor to clarify what is the "dry run".

The Agency also stated that in the previous version of the SAP issued on October 28, 2021, a backup plan by considering only treatment as a factor in the zero-inflated model for dealing with the convergence issue was already specified. Therefore, the Agency recommended the Sponsor reanalyze the key count secondary variables using the backup plan.

The Sponsor provided the Agency with the timeline for the SAP amendments and database lock for the APPLY-PNH and APPOINT-PNH studies and clarified that the final SAPs for these two trials were finalized prior to database lock. The Agency reminded the Sponsor that whether their analysis methods and results can be used for confirmatory evidence will be a review issue.

The Sponsor acknowledged the Agency's concerns and agreed to provide more information for their "dry run" as well as the finalized SAPs before database lock with future submissions.

The Sponsor stated that they are conducting additional analyses to support FACIT-Fatigue in APPLY-PNH to include in the NDA. The Agency reminded the Sponsor that a blinded trial is ideal to properly interpret results from a patient reported outcome (PRO). An open-label design is difficult to interpret as patients know if they are on study drug and this can influence how patients report symptoms. The Agency stated they would review additional analysis submitted to support FACIT-F during the NDA review.

Question 3: Does the Agency agree that the presented APPLY-PNH safety and tolerability data support registration of iptacopan in PNH patients?

FDA Response: You state that most adverse events (AEs) were mild or moderate in severity. There were no AEs leading to discontinuation, treatment interruption or deaths. Although serious infections were reported, no serious infection due to encapsulated bacteria was reported in either treatment arm. However, there was one infection caused by encapsulated bacteria (bronchitis due to Haemophilus influenzae) in the iptacopan arm. The most frequent AEs in the iptacopan arm compared to the C5 inhibitor arm were headache, diarrhea, and nasopharyngitis. There was one serious AE of a large increase in creatinine phosphokinase in the iptacopan arm that appears to be related to iptacopan.

The APPLY-PNH safety and tolerability data appear acceptable to support filing and subsequent review. Whether the safety data will support approval will be a review issue. You note that one subject in the iptacopan arm had an AE of bronchitis due to Haemophilus influenzae. Please clarify if the subject was vaccinated for Haemophilus influenzae; and if so, if the antibody titers.

Meeting Discussion: The Sponsor clarified that one patient had an adverse event of bronchitis due to Haemophilus influenzae despite receiving a vaccination for this organism, antibody titers were not collected. No other patients had an infection with an identified organisms for which they could be vaccinated against, this included meningococcal infections.

Question 4: Novartis would appreciate FDA's perspective on whether the risk of serious infection caused by encapsulated bacteria, and the requirement for vaccination against encapsulated bacteria prior to initiating iptacopan, can be managed through labeling and a communication plan, or if there is a need for a REMS with ETASU?

FDA Response: We note that subjects enrolled in the phase 3 studies were required to be vaccinated against Neisseria meningitidis infection and recommended to receive vaccination against Streptococcus pneumoniae and Haemophilus influenzae if available, at least 2 weeks prior to dosing. If treatment needed to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment was required to be taken from start of study until 2 weeks after completion of vaccination. Additionally, investigators and subjects (provided with a safety card) were advised to monitor for signs and symptoms of infections.

Due to the potential for an increased risk of infection caused by encapsulated bacteria associated with Factor B inhibition and the reported 2 serious SAEs of bacterial lobar pneumonia in PNH subjects treated with iptacopan to date, vaccination against encapsulated bacteria prior to initiating iptacopan and other risk mitigating measures to reduce this risk is important.

We refer you to the requirements of the Empaveli REMS on REMS@FDA which was recently approved to mitigate the occurrence and morbidity associated with encapsulated bacterial infections. The basic requirements of the Empaveli REMS might serve as a model for how your proposed REMS could be structured.

You should submit your REMS proposal with your NDA submission as early in the review cycle as possible. The initial submission should include the REMS document, supporting document, and materials to be appended to the REMS. For guidance on the appropriate format and content of the REMS, you may wish to refer to the draft guidance for industry, *Format and Content of a REMS Document*[1] in preparation of your submission which should be submitted in Module 1.16. A complete review of the proposed REMS including timing of assessment reports and knowledge, attitude, and behavior (KAB) surveys will occur in conjunction with the review of your NDA.

Meeting Discussion: No meeting discussion took place.

Question 5: Does the Agency agree with the updated proposal for the safety update to be submitted during NDA review?

FDA Response: The proposal for the safety update appears reasonable. You now plan to include data from pool 1a which includes phase 3 Study CLNP023C12302 (APPLY-PNH), phase 2 studies CLNP023X2201 and CLNP023X2204 (both phase 2 studies will be completed at the time of the NDA submission), Study CLNP023C12301 (APPOINT-PNH), and Study CLNP023C12001B, the roll over extension program study (PNH REP). In addition, you propose to include data from Pool 1b which includes safety data from completed and ongoing trials in other indications, 2203 (IgA nephropathy), X2202 (C3 glomerulopathy) and B12001B (C3 glomerulopathy extension).

As stated previously, we recommend you present safety data from APPLY-PNH separately in the clinical summary of safety as well as pooled. Also, present complement inhibitor naive subject safety data separate from complement experienced subject safety data for subjects with PNH.

Meeting Discussion: No meeting discussion took place.

Question 6: Does the Agency agree that data from the pivotal Phase III trial APPLY-PNH, with confirmatory evidence provided by efficacy data from the supportive Phase III study APPOINT-PNH and efficacy and mechanistic data from two PNH Phase II studies, are sufficient to support registration of iptacopan for the proposed indication of treatment of PNH in adult patients?

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

FDA Response: You propose to demonstrate substantial evidence of effectiveness based on data from the single phase 3 trial, APPLY-PNH, with mechanistic support as confirmatory evidence. Confirmatory evidence will be provided based on the efficacy results from the supportive phase 3 study APPOINT-PNH, which is a multicenter, open-label, single arm trial in 40 adults with PNH who are complement inhibitor naïve. Additional mechanistic support will be provided from the two PNH phase 2 studies (X2201, X2204).

Your proposal to demonstrate substantial evidence of effectiveness appears acceptable to support filing and subsequent review. Whether the data will support an indication for the treatment of PNH in adult patients will be a review issue. As Study APPLY-PNH is only in subjects previously on a C5 inhibitor you will need to provide compelling evidence (i.e., persuasive data from APPOINT-PNH, along with supportive data from your clinical development program) to receive an indication for treatment of all adult patients with PNH; ultimately this will be a review issue.

Meeting Discussion: The Sponsor presented topline data from the APPOINT-PNH study, in which adult patients with PNH who were naive to complement inhibitor therapy were treated with iptacopan. The Sponsor inquired if the Agency could share their initial view of the data in complement inhibitor naive patients from APPOINT-PNH in support of a broad indication.

The Agency informed the Sponsor that they have not been able to review the information provided as it was new information not included in the background package. While these results appear encouraging, the Agency cannot comment on the acceptability of the trial results to support a broader indication for patients with PNH. The Sponsor confirmed for the Agency that all the patients in the APPOINT-PNH study completed the 24 weeks, and that safety and efficacy datasets from the study will be submitted along with the CSR at the time of the initial NDA submission.

Question 7: Novartis would appreciate the Agency's perspective on the potential for priority review of the NDA on the basis of breakthrough therapy designation, compelling efficacy and favorable safety data which support the potential for iptacopan to address the unmet need for alternative treatment options that control both IVH and EVH, improve anemia and associated need for transfusion and provide an oral alternative to chronic injections?

FDA Response: Priority or standard review will be determined at the time of filing.

Meeting Discussion: The Sponsor inquired that based on the information provided can the Agency share initial thinking on possibility on providing priority

review and if they can provide any additional information to help support this request.

The Agency stated based on the information provided in the meeting package, it is likely the Sponsor would receive priority review, but reiterated that priority or standard review will be determined at the time of filing.

Question 8: Since the APPOINT-PNH study will now be included in the NDA, the previously agreed content/format proposal has been updated accordingly. Novartis has also provided a clarification in response to the Type B Meeting feedback received on September 8, 2022. Does the Agency agree with the update to the proposed content of the NDA?

FDA Response: The update to the proposed content appears reasonable. You are proposing to include safety and efficacy data from APPOINT-PNH in your NDA submission. You are not planning on pooling efficacy data given differences in the patient population and study design. You propose to include the safety results in pool 1a.

Meeting Discussion: No meeting discussion took place.

Question 9: Does the Agency anticipate an Advisory Committee meeting will be held during the review of the PNH application?

FDA Response: The need for an Advisory Committee meeting will be determined during the NDA review.

Meeting Discussion: The Sponsor asked if the Agency had any concerns that would warrant an Advisory Committee (AC) meeting.

The Agency stated the need for an AC has not been identified based on the information provided in the meeting package but reiterated the need for an AC meeting will be determined during the NDA review.

The Sponsor also confirmed that they intend on submitting a full submission for review with no rolling components.

Question 10: Novartis seeks clarification from the Agency about their expectations regarding facility information that should be included in the original NDA as part of Module 3 and Form FDA 356h. Specifically, does the Agency agree that facilities (b) (4) do not need to be listed in Module 3 as well as Form FDA 356h?

FDA Response: We refer you to the guidance for industry *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER*

Questions and Answers. **The Guidance recommends** (b) (4) **covered by FDA's ICH guidance *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*[1] be listed in Form FDA 356h of the application. Since ICH Q7 covers warehousing of the API and intermediates, the warehousing facilities for these materials should be included in Form 356h and also in Module 3. The warehousing facilities for materials for which the disposition decision has been made (e.g., released or rejected) do not need to be listed in the application.**

In uncertain cases, the Guidance recommends adding the sites to Module 3 to ensure timely review of the application (Question 2 of Module 3 Questions/Answers).

Meeting Discussion: No meeting discussion took place.

Additional Comments
Regarding the APPOINT-PNH (CLNP023C12301) trial, we noted (b) (4) **However, on clinicaltrials.gov[2], we found that the actual primary completion date of the trial is November 2, 2022.** (b) (4) **We remind you that any changes made to the analysis methodologies based on analyses of data after the completion of the trial can only be considered for post-hoc and exploratory purposes.**

3.0 ADDITIONAL IMPORTANT INFORMAITON

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that you should submit your REMS proposal with your NDA submission
- Major components of the application are expected to be submitted with the

[2] https://clinicaltrials.gov/ct2/show/NCT04820530

original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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

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

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.

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No Action items.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor presentation.

40 Pages 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/

CARRIE E DIAMOND
01/12/2023 03:53:57 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND #	134655
Request Receipt Date	10/28/2020
Product	Iptacopan (LNP023)
Indication	For the treatment of Paroxysmal nocturnal hemoglobinuria
Drug Class/Mechanism of Action	Small Molecule/ Selective protease inhibitor that inhibits C3 and C5 convertases thereby blocking the formation of the MAC
Sponsor	Novartis Pharmaceuticals Corporation
ODE/Division	Nonmalignant Hematology
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	12/24/2020

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

For the treatment of patients with hemolytic paroxysmal nocturnal hemoglobinuria (PNH).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

PNH is a rare and potentially life-threatening disease defined by the increased activation of the complement system causing destruction of the red blood cell membrane. Features of the disorder include thrombophilia, chronic hemolytic anemia and pancytopenia. Thromboembolism is the leading cause of morbidity and mortality in patients with PNH. The other causes of death include hemorrhage, renal failure, cardiac failure, infections, myelodysplastic syndrome and aplastic anemia. The only cure for certain types of PNH is hematopoietic stem cell transplantation which comes with a relatively high risk of morbidity.

LNP023 is a potent and highly selective inhibitor of complement factor B, a key protease of the alternative complement pathway. Intervening upstream from C5 of the complement cascade with LNP023 is hypothesized to provide improved efficacy compared to C5 only inhibitor therapy by inhibiting both intravascular hemolysis and C3-mediated extravascular hemolysis.

The two other therapies for PNH are C5 inhibitors. Extravascular hemolysis eventually emerges once the therapeutic inhibition with anti-C5 agents prevents intravascular hemolysis. These patients remain anemic and transfusion dependent, even though their transfusion requirements may decrease. Currently, there is no therapeutic option available to prevent C3-mediated extravascular hemolysis. Breakthrough hemolysis has also been seen with one C5 inhibitor. There is a rare polymorphism at the eculizumab binding site of C5 that results in eculizumab non-responders. The availability of an oral PNH therapy would significantly reduce patient burden of parenteral administration, with the potential to improve patient quality of life.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

The primary endpoint in trial CLNP023X2201 is reduction of chronic hemolysis as measured by LDH reduction. Secondary endpoints include safety and tolerability, pharmacokinetics of LNP023, and markers of intra-and extravascular hemolysis (including hemoglobin). In trial CLNP023X2204, the primary endpoint is the same. The secondary endpoints are to assess the **dose response effect on reduction of hemolysis**, safety and tolerability, pharmacokinetics of LNP023 markers of intra-and extravascular hemolysis.

The clinical benefit endpoint in PNH is “transfusion independence”.
Endpoints that are reasonably likely to predict clinical benefit of a drug in PNH include hemoglobin stabilization and reduction of intravascular hemolysis assessed by LDH levels.

The pivotal studies supporting traditional approval of eculizumab and ravulizumab have used primary efficacy endpoints of transfusion independence, hemoglobin stabilization and reduction of intravascular hemolysis assessed by LDH levels.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s)

used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Generic Name	Trade Name	Endpoint	Treatment Effect	Intended Population
eculizumab	Soliris	Patients with hemoglobin stabilization	49% Soliris vs. 0% Placebo	patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
ravulizumab	Ultomiris	Transfusion avoidance and hemolysis as directly measured by normalization of LDH levels.	TA - Ultomiris 73.6% vs.Soliris 66.1%. LDH normalization - Ultomiris 53.6% vs. Soliris 49.4%	adult patients with paroxysmal nocturnal hemoglobinuria (PNH)

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

(b) (4)

[redacted]

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Trial	**Phase**	**Trial Design**	**Endpoints**	**Treatment groups**	**Number of subjects**	**Trial results**
CLNP023X2201 (ongoing)	2	open label, single arm, multiple dose study to assess efficacy, safety, pharmacokinetics and pharmacodynamics	1º: reduction of chronic hemolysis as measured by LDH reduction	LNP023 200 mg and eculizumab/LNP023 50 or 200 mg and eculizamab	PNH (n=15 planned, 16 enrolled)	•100% of patients (10) had a reduction in LDH from 34-81% •10 patients with improvement in hemoglobin from 15-60%
CLNP023X2204 (ongoing)	2	multi-center, randomized, open-label, efficacy, safety, pharmacokinetics and pharmacodynamics study, assessing multiple LNP023 doses	1º: reduction of chronic hemolysis as measured by serum LDH response rate	LNP023 100mg/LNP023 200 mg	PNH (n=10 planned, 13 randomized)	•100% of patients (7) had at least a 60% reduction in LDH at week 4 •7 patients did not require transfusions with Hb increase in most
CLNP023C12302 (planned)	3	Randomized, multicenter, activecomparator controlled, open label trial to evaluate efficacy and safety of oral LNP023 in adult participants with PNH with residual anemia, despite		LNP023/ eculizumab or ravulizumab	PNH (n~91)	

		treatment with an anti- C5 antibody				
CLNP023C12301 (planned)	3	A multicenter, singlearm, open-label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult PNH patients who are naive to complement inhibitor therapy		LNP023	PNH (n=40)	
CLNP023C12001B (planned)	3B	Open label study to provide access to LNP023 for PNH patients who have completed Phase-2 and Phase-3 studies with LNP023		LNP023	PNH (n~160)	

In trial CLNP023X2201, interim results at week 13 showed 100% of patients (10) had a reduction in LDH from 34-81%. All patients had improvement in hemoglobin from 15-60% without RBC transfusions and prolonged survival of PNH red blood cells. In this trial, LNP023 was added to eculizamab.
In trial CLNP023X2204, LNP023 was given to patients with PNH who were complement inhibitor treatment naïve (no less than 3 months). All 7 patients had at least a 60% reduction in LDH at week 4. No patients required a RBC transfusion. However, between the 2 sequences, 3 patients were not able to reach/sustain hemoglobin at LLN within the 13 weeks shown.

In the human ADME study (CLNP023A2101), three of the 6 patients reported 8 mild AEs, 4 (in 2 subjects) were reported as suspected to be related to LNP023 (two fatigue events, oral herpes and headache). Other potential safety risks apparent from the pre-clinical program with LNP023 are testicular effects, bone marrow toxicity with severe anemia and thyroid dysfunction. These were not seen in later trials with patients with PNH but are still carefully monitored for.

Patients have to be vaccinated against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae at least 4 weeks prior to first dosing with LNP023 due to the mechanism of action and concern for infection with encapsulated organisms. No infections with encapusulated organisms have been found.

Two patients have discontinued treatment due to adverse events. One discontinuation was due to a non-serious AE of headache in a patient with PNH who received two days of 50 mg twice daily LNP023 in study CLNP023X2204. The other discontinuation occurred after the interim analysis and was due to a SAE, lymphoproliferative disorder in study CLNP023X2201, which started after 11 months of treatment with LNP023 200 mg twice daily. Immunosuppression is a risk factor for this event, and so the event was considered possibly related to treatment with LNP023, however, the patient had severe lymphopenia (lymphocytes 0.2 $x10^9$/L) at study entry and had been taking eculizumab for the past 12 years and was on a high dose, 1500 mg, at study entry.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

In the sponsor's phase 2 trials where LNP023 was added to the regimen of eculizumab or given alone, all 17 subjects had improvement in LDH and transfusion requirements. These endpoints were also used for the approved drugs, eculizumab and ravulizamab. In trial CLNP023X2201 (n=10), 100% of patients with LDH reduction from 34-81%, 100% of patients with hemoglobin increases from 15-60% with no RBC transfusions required. These results were sustained even after 7/10 patients discontinued eculizumab. Graphical data sent in by the sponsor shows continued response (decrease in LDH) of patients, including those for whom eculizumab was discontinued, through day 500. In trial CLNP023X2204 (n=7), 100% of patients with LDH reduction ≥60% and no RBC transfusions were required. Both studies, describe baseline charteristics of the patients as being transfusion dependent. In addition, both studies include extension phases of 2-3 years. These results show that LNP023 could benefit patients with PNH who are not responding well to a C5 inhibitor alone. Decreased hemolysis and a decrease in the need for transfusions may improve the quality of life for these patients with PNH.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division recommends continued development of LNP023 for PNH.

The sponsor is encouraged to clearly define subjects who are treatment naïve and if any history of a complement inhibitor would affect trial results. The transfusion history of each patient should be clearly stated.

We requested that the sponsor, for trial CLNP023X2204, provide treatment histories for the six patients with treatment beyond 1 week (include all but (b) (6)). We would like to assess what might explain the inability to reach/sustain their hemoglobins at the LLN for patient (b) (6) in sequence 1 and patients (b) (6) and (b) (6) in sequence 2. Please include the length of time off of any previous C5 inhibitor treatment for these patients.
In response, the sponsor stated that patient (b) (6) had a prior history of myelodysplastic syndrome and patient (b) (6) did reach LLN by week 8 of treatment. In addition, though patient (b) (6) did not reach LLN for hemoglobin, like the other two patients he remained transfusion-independent after starting the drug which is an improvement and satisfies the clinical benefit endpoint.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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/

DONNA A WHYTE-STEWART
12/01/2020 02:19:28 PM

VIRGINIA E KWITKOWSKI
12/01/2020 02:20:48 PM

ANN T FARRELL
12/01/2020 02:23:13 PM