

## Title Page

**Protocol Title:** A Phase 2b Pivotal Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Non-infectious, Intermediate-, Posterior- or Pan-uveitis

**Protocol Number:** 21103

**Protocol Version:** 5.3

**Protocol Date:** 11 October 2024

**Compound:** Izokibep

**Brief Title:** Phase 2b Study of Izokibep in Non-infectious, Intermediate-, Posterior- or Pan-uveitis

**Study Phase:** Phase 2b

**Sponsor Name:** ACELYRIN, INC.

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| Global 5.0      | 09 October 2024  |

**Protocol Amendment Summary of Changes Table**

The key changes to Global Version 5.0 dated 09 October 2024 reflected in this CSP Europe are summarized below.

| Section # and Name                                   | Description of Change                                                                                                                                                                                                                                                                              | Brief Rationale                                                                        |
|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| 1.1 Synopsis, 3 Objectives, Endpoints and Estimands, | Changed the timing of the primary efficacy endpoint from “occurring at or after week 10 and up to week 52” to “up to week 52”.                                                                                                                                                                     | To align with past regulatory accepted primary endpoint for time to treatment failure. |
| 1.1 Synopsis, 3 Objectives, Endpoints and Estimands, | Changed a criteria for the secondary endpoint of quiescence, from no active lesions to no new inflammatory lesions.                                                                                                                                                                                | To align with past regulatory accepted endpoint pertaining to quiescence.              |
| 9.3.2 Primary Endpoint and Estimand                  | Updated the definition of the primary endpoint, “Time to Treatment Failure” to include non-response up to week 10 as an event. Also updated the analysis population for the primary endpoint from subjects with uveitis who did not meet the criteria for non response to all subjects randomized. | To align with past regulatory accepted endpoint pertaining to quiescence.              |

The key changes to Global Version 4.0 dated 16 August 2024 reflected in this CSP Europe are summarized below.

| <b>Section # and Name</b>                                                                                                                                                                                                      | <b>Description of Change</b>                                                                                                                                                    | <b>Brief Rationale</b>                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| Title Page                                                                                                                                                                                                                     | Replaced the EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) number with European Union (EU) Clinical Trial number.<br>Updated sponsor signatory. | Sponsor approver has changed.                                                                                                                           |
| 1.1 Synopsis,<br>3 Objectives,<br>Endpoints and<br>Estimands,<br>9.1 Statistical<br>Hypotheses,<br>9.1.1<br>Multiplicity<br>Adjustment<br>and Type I<br>Error Rate,<br>and<br>9.3.3<br>Secondary<br>Endpoints and<br>Estimands | Downgraded the quiescence secondary objective and endpoint.                                                                                                                     | To prioritize endpoints associated with uveitis inflammation and subject reported vision-targeted health status.                                        |
| 1.1 Synopsis<br>and<br>4.1.1<br>Independent<br>Data<br>Monitoring<br>Committee                                                                                                                                                 | Updated frequency of data monitoring committee (DMC) meetings every 6 months to more flexible language.                                                                         | Added flexibility to the frequency of DMC meetings, to allow for meetings less frequent than every 6 months.                                            |
| 1.3 Schedule<br>of Activities                                                                                                                                                                                                  | Corrected the typographical error ‘d’ on the week 59 Follow-up visit for the procedure: Intraocular pressure.                                                                   | Corrected the typographical error “d” in the Schedule of Activities (SoA) table for the procedure: Intraocular pressure on the week 59 Follow-up visit. |

| Section # and Name                                                    | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Brief Rationale                                                                                                                                           |
|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Exclusion criterion 30 of Section 5.2 and 6.8.2 Concomitant Therapies | Replaced '3 mg/day' with '3 g/day'.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Corrected the error on mycophenolate mofetil dosage.                                                                                                      |
| 6.1.1 Dosage, Administration and Schedule: Izokibep and Placebo       | Replaced '1 of 4 dosing groups' with '1 of 2 dosing groups'.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Corrected the error on number of dosing groups used in the latter part of the study.                                                                      |
| 6.8.2 Concomitant Therapies                                           | Deleted text related to potential effects of izokibep on other drugs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | No drug interactions are known, and no pharmacokinetic interactions are anticipated based on the unique albumin-binding site and protein metabolic route. |
| 7.1 Discontinuation of Study Drug                                     | Updated the reasons for removal of a subject from the study drug.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Improved the clarity and readability of the reasons for discontinuation of study drug.                                                                    |
| 7.1.1 Liver Chemistry Stopping Criteria, Figure 2                     | Corrected the liver chemistry stopping criteria from "cannot be monitored weekly for 4 weeks" to "cannot be monitored twice weekly for 4 weeks".                                                                                                                                                                                                                                                                                                                                                                                                      | Corrected the error in the figure.                                                                                                                        |
| 8.3.6 Adverse Events of Special Interest                              | <p>Clarified that major adverse cardiovascular and cerebrovascular events includes cerebrovascular accident and transient ischemic attack, non-fatal myocardial infarction, or unstable angina, cardiovascular death.</p> <p>Clarified that for infections, only those that are opportunistic, serious, or fungal are included as adverse events of special interest.</p> <p>Clarified that cytopenias includes anemia, neutropenia, lymphopenia, monocytopenia, thrombocytopenia.</p> <p>Updated to include systemic hypersensitivity reactions.</p> | Improved the clarity of the definitions for events that qualify as adverse events of special interest.                                                    |

| Section # and Name                                 | Description of Change                                                                                                                                                                                                              | Brief Rationale                                                                                                                   |
|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| 10.3.3<br>Recording and Follow-up of AE and/or SAE | Updated 'Assessment of Intensity' to 'Assessment of Severity'.<br>Updated that assessment of adverse event (AE) and serious adverse event (SAE) will be as per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. | Change made to replace intensity (mild, moderate, or severe) with CTCAE grading version 5.0 to align with other izokibep studies. |
| Global                                             | Minor editorial and document formatting revisions.                                                                                                                                                                                 | Administrative change.                                                                                                            |
| Global                                             | Version and date were revised on the title page and in the header throughout the document.                                                                                                                                         | Administrative change.                                                                                                            |

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## 1. Protocol Summary

### 1.1. Synopsis

**Protocol Title:** A Phase 2b Pivotal Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Non-infectious, Intermediate-, Posterior- or Pan-uveitis

**Brief Title:** Phase 2b Study of Izokibep in Non-infectious, Intermediate-, Posterior- or Pan-uveitis

**Rationale:** Izokibep is a small protein molecule that acts as a selective, potent inhibitor of interleukin-17A, to which it binds with high affinity. This study investigates izokibep in subjects with active non-infectious, intermediate-, posterior- or pan-uveitis requiring high-dose steroids.

#### Overall Design:

This is a Phase 2b pivotal, multi-center, randomized, double-blind, placebo-controlled dose-finding study. The aim is to investigate the efficacy, safety and immunogenicity of izokibep in subjects with active non-infectious, intermediate-, posterior- or pan-uveitis in at least 1 eye despite at least 2 weeks of prednisone/prednisolone 7.5 mg/day to 40 mg/day inclusive (or corticosteroid equivalent).

This study will be conducted at study sites in North America and Europe. Additional sites and regions may be added.

#### Objectives and Endpoints:

| Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Endpoints                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>To demonstrate that izokibep is efficacious compared to placebo, as measured by time to treatment failure up to week 52</li> </ul>                                                                                                                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>Time to treatment failure</li> </ul>                                                                            |
| <b>Secondary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                        |
| <p>To demonstrate that izokibep is efficacious, as measured by:</p> <ul style="list-style-type: none"> <li>Change in BCVA from best state achieved before week 10 to week 24</li> <li>Change in the NEI-VFQ-25 score from best state achieved before week 10 to week 24</li> <li>Change in central retinal thickness (by SD-OCT) from baseline to week 10</li> <li>Change in central retinal thickness (by SD-OCT) from best state achieved <math>\leq</math> week 10 up to week 52</li> </ul> | <ul style="list-style-type: none"> <li>BCVA</li> <li>NEI-VFQ-25 score</li> <li>Central retinal thickness</li> <li>Central retinal thickness</li> </ul> |

| Objectives                                                                                                                                                                             | Endpoints                                                                                                                                                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Proportion of subjects that achieve quiescence at week 10</li> </ul>                                                                            | <ul style="list-style-type: none"> <li>Quiescence</li> </ul>                                                                                                    |
| To assess the safety and tolerability of izokibep as measured by the incidence of TEAEs, events of special interest, SAEs and clinically significant laboratory values and vital signs | <ul style="list-style-type: none"> <li>TEAEs, events of special interest and SAEs</li> <li>Laboratory values and vital signs at collected timepoints</li> </ul> |
| To assess the immunogenicity of izokibep as measured by the presence of treatment-emergent ADAs                                                                                        | <ul style="list-style-type: none"> <li>ADAs</li> </ul>                                                                                                          |

ADAs = anti-drug antibodies; BCVA = best corrected visual acuity; NEI = National Eye Institute; SAE = serious adverse event; SD-OCT = Spectral-Domain Optical Coherence Tomography; TEAE = treatment-emergent adverse event; VFQ-25 = Visual Function Questionnaire-25

## Endpoint Definitions

### Treatment Failure

| Endpoint/Parameter                                                       | Non-response                                                                                                                                                         | Treatment Failure                                                                                                                      |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
|                                                                          | At any visit from week 4 up to but not including week 10, a subject is defined as a non-responder by meeting at least 1 of the following criteria in at least 1 eye: | At or after week 10, a subject is defined as reaching treatment failure by meeting $\geq 1$ of the 4 criteria below in at least 1 eye: |
| Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions | New active, inflammatory lesions, or worsening of previously identified inflammatory lesions, relative to baseline                                                   | New active, inflammatory lesions, or worsening of previously identified inflammatory lesions, relative to baseline                     |
| ACC count (SUN Grade)                                                    | $\geq 1$ -grade increase (worsening) from baseline                                                                                                                   | 2-step increase relative to the best state achieved up to week 10 <sup>a</sup>                                                         |
| Vitreous haze (NEI/SUN Grade)                                            | $\geq 1$ -grade increase (worsening) from baseline                                                                                                                   | 2-step increase relative to the best state achieved up to week 10 <sup>a</sup>                                                         |
| Visual acuity (ETDRS)                                                    | Worsening of BCVA by $\geq 15$ letters (not due to cataract) relative to the best state achieved                                                                     | Worsening of BCVA by $\geq 15$ letters (not due to cataract) relative to the best state achieved up to week 10                         |

ACC = anterior chamber cell; BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI = National Eye Institute; SUN = Standardization of Uveitis Nomenclature

<sup>a</sup> A 2-step increase is represented by a change of Grade 0 to Grade 2+ or Grade 0.5+ to Grade 3+.

Quiescence<sup>a</sup>

|                                                                          |                             |
|--------------------------------------------------------------------------|-----------------------------|
| <b>Quiescence (both eyes)</b>                                            |                             |
| Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions | No new inflammatory lesions |
| ACC Count (SUN Grade)                                                    | Trace or absent (0.5+ or 0) |
| Vitreous Haze (NEI/SUN Grade)                                            | Trace or absent (0.5+ or 0) |

ACC = anterior chamber cell; NEI = National Eye Institute; SUN = Standardization of Uveitis Nomenclature

<sup>a</sup> Quiescence requires that the 3 criteria be met for both eyes.

**Brief Summary:**

Approximately 100 subjects with active non-infectious, intermediate-, posterior- or pan-uveitis despite at least 2 weeks of prednisone/prednisolone 7.5 mg/day to 40 mg/day (or corticosteroid equivalent) will be enrolled. The study consists of up to a 28-day (4-weeks) screening period, a 51-week treatment period and a follow-up period with visits at 8 weeks and 14 weeks after the last dose of study drug to assess safety and immunogenicity. Maximum study duration for an individual subject is approximately 69 weeks.

Eligible subjects will be randomized into 1 of 2 groups in a **CC** ratio as follows:

- Group 1: placebo subcutaneous (SC) once weekly (QW)
- Group 2: izokibep SC **CCI** QW

Of the approximately 100 subjects to be enrolled, approximately 20 are attributed to those enrolled under previous versions of the protocol (ie, previously included every 2 weeks [Q2W] arms), with an additional approximately 80 subjects (40/arm) to be enrolled in the QW arms. Randomization will be stratified by any prior treatment with a systemic tumor necrosis factor-alpha inhibitor (yes/no) and concomitant systemic inflammatory disease (yes/no). The first dose of study drug will be administered at day 1 (week 0).

In addition, all subjects will receive a standardized prednisone/prednisolone burst of 60 mg/day from day 1 up to day 14 (week 0 to week 1). Beginning at week 2, subjects will undergo a protocol-defined mandatory taper schedule which will decrease their dosage until they are off oral prednisone/prednisolone by week 15. Subjects who enter the study on topical corticosteroids (eye drops) will undergo a standardized taper schedule beginning at week 1 until all subjects are off topical corticosteroids by week 10. Depending on the dose that the subject is on at study entry, the number of drops per day will be decreased every week at predefined increments.

The last dose of study drug will be administered at week 51.

Analysis of the primary efficacy endpoint will occur after all subjects have had the opportunity to complete the week 24 visit or terminate early from the study.

**Number of Subjects:**

Approximately 100 subjects will be enrolled in the study, with enrollment continuing until approximately 40 subjects have been enrolled into each QW treatment arm.

**Intervention Groups and Duration:**

- Group 1 CCI : placebo SC QW from day 1 (week 0) to week 51
- Group 2 CCI : izokibep SC CCI QW from day 1 (week 0) to week 51

Izokibep and matching placebo will be visually indistinguishable to prevent unblinding during preparation or administration of study material.

Subjects assigned to receive placebo or active, administered QW, will be randomized in a CC ratio. Study drug doses are fixed and will not be adjusted for individual subjects during the study.

**Data Monitoring:**

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

The DMC will consist of at least 1 medical expert with the relevant therapeutic area expertise and at least 1 statistician and will have a minimum of 3 members, 1 of whom will serve as the Chair. The DMC responsibilities, members (including their qualifications and possible conflicts of interest), authorities, meeting frequency to review unblinded interim data, and procedure will be documented in the DMC charter. The committee will meet as needed as outlined in the DMC charter. After each review, the DMC will make recommendations regarding the continuation of the study based on safety. The DMC may review unblinded efficacy data when all subjects have had the opportunity to complete the week 10 visit. The DMC may make a recommendation on further development activities for izokibep based on this data review. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The study team operationalizing the day-to-day of the study, the subjects and the investigators will remain blinded to these interim results until after the study is completed.

**Statistical Considerations:**

Estimands for efficacy analyses will be defined using the treatment policy strategy for intercurrent events. All treated subjects will contribute to safety analyses.

For comparisons of izokibep to placebo, subjects receiving the QW regimen of izokibep will be compared to the combined group of subjects receiving either regimen of placebo. Subjects receiving the Q2W regimen of izokibep, enrolled before amendment v2.0, will be listed but not included in summaries or comparisons.

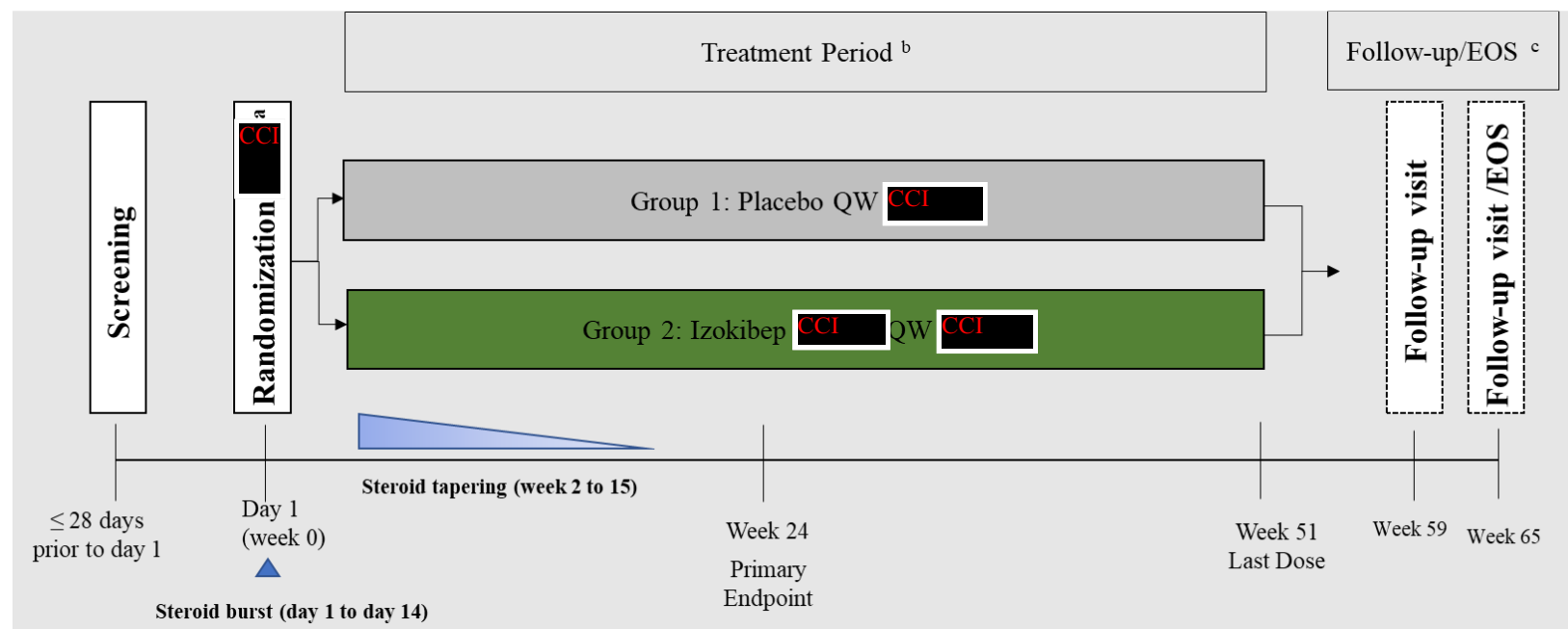
Hypotheses will be tested sequentially, starting with the primary efficacy endpoint and moving through the secondary endpoints in the order listed. Within each endpoint, the izokibep QW dosing regimen will be compared to the combined placebo group. As long as all prior comparisons yield  $p < 0.0499$ , subsequent hypotheses will be reported at the  $\alpha = 0.050$  level; if a hypothesis is not rejected, subsequent hypotheses will not be tested (but p-values will be reported for descriptive purposes).

Time to treatment failure will be analyzed using all available data through week 52, with the primary analysis reported after the last subject passes week 24. Subjects who discontinue the study without experiencing treatment failure will be treated as censored at the time of last assessment.

Best corrected visual acuity and National Eye Institute-Visual Function Questionnaire data will be compared with a repeated measures mixed model including terms for treatment, timepoint, treatment by timepoint interaction and the stratification factors employed for randomization. Quiescence at week 10 will be compared with a stratified test of response rate differences, using the strata employed for randomization.

Safety data will be summarized. Adverse events, serious adverse events and laboratory data will be summarized.

## 1.2. Schema



EOS = end of study; QW = once weekly; TNF- $\alpha$  = tumor necrosis factor-alpha

<sup>a</sup> Randomization will be stratified by any prior treatment with a systemic TNF- $\alpha$  inhibitor (yes/no) and concomitant systemic inflammatory disease (yes/no).

<sup>b</sup> All subjects will receive a standardized prednisone/prednisolone burst of 60 mg/day from day 1 (week 0) to day 14. By week 2, subjects must undergo a protocol-defined oral steroid taper schedule which will decrease their dosage until they are off oral prednisone/prednisolone by week 15. Subjects who enter the study on topical corticosteroids (eye drops) will undergo a standardized taper schedule beginning on week 1 until all subjects are off topical steroids by week 10.

<sup>c</sup> Two follow-up visits will be completed by all subjects at week 59 ( $\pm 5$  days) and week 65 ( $\pm 5$  days). For subjects who terminate early, the follow-up visits should be completed at 8 weeks ( $\pm 5$  days) and 14 weeks ( $\pm 5$  days) after the last dose of study drug.

### 1.3. Schedule of Activities

| Procedures                                                          | Screen             | Treatment Period (weeks ± 3 d) <sup>a</sup> |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    | Follow-up <sup>b</sup> |  |
|---------------------------------------------------------------------|--------------------|---------------------------------------------|---|---|---|---|---|----------------|----|----|----|----------------|----|----|----|----|----|----|-----------------------|----|------------------------|--|
|                                                                     | ≤ 28 d prior to d1 | 0 (d1)                                      | 1 | 2 | 3 | 4 | 8 | 10             | 12 | 16 | 20 | 24             | 28 | 32 | 36 | 40 | 44 | 48 | 52 or ET <sup>c</sup> | 59 | 65                     |  |
| Informed consent                                                    | X                  |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Eligibility criteria <sup>d</sup>                                   | X                  | X                                           |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Demography                                                          | X                  |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Physical exam                                                       | X                  | X <sup>e</sup>                              |   |   |   |   |   | X <sup>e</sup> |    |    |    | X <sup>e</sup> |    |    |    |    |    |    | X                     |    |                        |  |
| Weight                                                              | X                  | X                                           |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Height                                                              | X                  |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Medical and medication history (including alcohol and nicotine use) | X                  | X                                           |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Vital signs <sup>f</sup>                                            | X                  | X                                           | X | X | X | X | X | X              | X  | X  | X  | X              | X  | X  | X  | X  | X  | X  | X                     | X  |                        |  |
| 12-lead ECG <sup>g</sup>                                            | X                  |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Chest x-ray <sup>h</sup>                                            | (X)                |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| AE reporting <sup>i</sup>                                           |                    |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| SAE reporting <sup>i</sup>                                          | X                  |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Prior and concomitant medication                                    |                    |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| Efficacy Assessments                                                |                    |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |
| CCI                                                                 |                    |                                             |   |   |   |   |   |                |    |    |    |                |    |    |    |    |    |    |                       |    |                        |  |

| Procedures                                      | Screen             | Treatment Period (weeks ± 3 d) <sup>a</sup> |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    | Follow-up <sup>b</sup> |  |
|-------------------------------------------------|--------------------|---------------------------------------------|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|-----------------------|----|------------------------|--|
|                                                 | ≤ 28 d prior to d1 | 0 (d1)                                      | 1 | 2 | 3 | 4 | 8 | 10 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 or ET <sup>c</sup> | 59 | 65                     |  |
| CCI                                             |                    |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| CCI                                             | X                  |                                             |   |   |   |   |   | X  |    |    |    | X  |    |    |    |    |    |    | X                     |    |                        |  |
| Evaluation of non-response <sup>1</sup>         |                    |                                             |   |   |   | X | X |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Evaluation of quiescence                        |                    |                                             |   |   |   |   |   | X  |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Evaluation of treatment failure <sup>1</sup>    |                    |                                             |   |   |   |   |   | X  | →  |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| BCVA <sup>m</sup>                               | X                  | X                                           |   |   |   | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X                     |    |                        |  |
| VFQ-25 (interviewer-administered) <sup>m</sup>  |                    | X                                           |   |   |   | X |   | X  |    |    |    | X  |    |    | X  |    |    |    | X                     |    |                        |  |
| CCI                                             |                    |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    | X                     |    |                        |  |
| CCI                                             |                    |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Laboratory Tests                                |                    |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Serology (Hep B, HCV) <sup>n</sup>              | X                  |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Syphilis testing                                | X                  |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| TB test <sup>o</sup>                            | X                  |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Thyroid function tests <sup>o</sup>             | X                  |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| ANA/anti-ds DNA                                 | X                  |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Herpes simplex virus and Varicella zoster virus | X                  |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Human immunodeficiency virus test               | X                  |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |

| Procedures                                                    | Screen             | Treatment Period (weeks ± 3 d) <sup>a</sup> |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    | Follow-up <sup>b</sup> |  |
|---------------------------------------------------------------|--------------------|---------------------------------------------|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|-----------------------|----|------------------------|--|
|                                                               | ≤ 28 d prior to d1 | 0 (d1)                                      | 1 | 2 | 3 | 4 | 8 | 10 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 or ET <sup>c</sup> | 59 | 65                     |  |
| Hematology/chemistry                                          | X                  | X                                           |   |   |   | X |   | X  |    | X  |    | X  |    |    | X  |    | X  |    | X                     | X  |                        |  |
| Serum electrolyte and glucose monitoring                      |                    |                                             |   | X |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Hemoglobin A1c                                                |                    | X                                           |   |   |   |   |   |    |    |    |    | X  |    |    |    |    |    |    | X                     |    |                        |  |
| Urinalysis                                                    | X                  | X                                           |   |   |   | X |   | X  |    | X  |    | X  |    |    | X  |    | X  |    | X                     | X  |                        |  |
| C-reactive protein                                            | X                  | X                                           |   |   |   | X |   | X  |    | X  |    | X  |    |    | X  |    | X  |    |                       |    |                        |  |
| Pregnancy test (WOCBP only) <sup>p</sup>                      | X                  | X                                           |   |   |   | X | X |    | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X                     | X  |                        |  |
| PK sampling <sup>q</sup>                                      |                    | X                                           |   |   |   | X |   | X  |    |    |    | X  |    |    | X  |    |    |    | X                     | X  | X                      |  |
| CCI                                                           |                    |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| CCI                                                           |                    |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
|                                                               |                    | X                                           |   |   |   |   |   | X  |    |    |    | X  |    |    |    |    |    |    |                       |    |                        |  |
| Treatment Assignment                                          |                    |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Treatment assignment/ randomization                           |                    | X                                           |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Study Drug Administration and Dosing Diary                    |                    |                                             |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| QW dosing (at site) <sup>a, s</sup>                           |                    | X                                           | X | X | X | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  |                       |    |                        |  |
| Dosing diary <sup>t</sup>                                     |                    |                                             |   |   |   | → |   |    |    |    |    |    |    |    |    |    |    |    |                       |    |                        |  |
| Prednisone/prednisolone treatment and dispensing <sup>u</sup> |                    | X                                           | X | X | X | X | X | X  | X  |    |    |    |    |    |    |    |    |    |                       |    |                        |  |

ACC = anterior chamber cell; CCI = central corneal injury; AE = adverse event; ANA = antinuclear antibodies; anti-ds DNA = anti-double-stranded deoxyribonucleic acid; BCVA = best corrected visual acuity; d = day; ECG = electrocardiogram; CCI = central corneal injury; ET = early termination; CCI = central corneal injury; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL = high-density lipoprotein; Hep B = hepatitis B; PCR = polymerase chain reaction; PK = pharmacokinetic; PPD = purified protein derivative; QW = once weekly; SAE = serious adverse event; CCI = central corneal injury

CCI [REDACTED]; TB = tuberculosis; VFQ-25 = Visual Function Questionnaire-25; WOCBP = women of childbearing potential.

<sup>a</sup> Visit/dosing windows of  $\pm 3$  days on either side of the scheduled visits/dosing are permitted; however, the investigator should try to keep the subjects on the original visit/dosing schedule. The window of  $\pm 3$  days is relative to day 1 and applicable for all subsequent visits/dosing. The minimum time between doses should be no less than 4 days and no more than 10 days. In case of a delayed or missed dose, the investigator should return subjects on the original visit/dosing schedule in relation to day 1 for subsequent doses.

<sup>b</sup> The follow-up period consists of 2 visits: an 8-week follow-up visit ( $\pm 5$  days) after the last dose of study drug will be completed by all subjects for safety and collection of pregnancy information. In addition, a 14-week follow-up visit will be completed ( $\pm 5$  days) for collection of PK and ADA samples.

<sup>c</sup> Subjects that end the study early will complete an ET visit and complete the procedures described at the week 52 visit within 2 weeks of the last dose of study drug.

<sup>d</sup> If a subject has ocular findings suggestive of undiagnosed sarcoidosis (ie, granulomas) during screening, the subject should be evaluated. Eligibility determination should occur following confirmation that concomitant medications will not be changed, and no prohibited medications will be initiated.

<sup>e</sup> Inclusive of skin/mucus membrane inspection.

<sup>f</sup> Vital signs include measurements of temperature, respiratory rate, systolic and diastolic blood pressure and pulse. Measurements should be taken in a sitting position after 5 minutes' rest.

<sup>g</sup> Electrocardiograms in triplicate will be recorded after the subject has been supine for at least 5 minutes.

<sup>h</sup> Chest x-ray required only for subjects with a positive or indeterminate QuantiFERON<sup>®</sup> who do not have a chest x-ray available within 3 months of screening as indicated in [Section 5.2](#). Women of childbearing potential must have negative pregnancy test before x-ray is performed.

<sup>i</sup> Serious adverse events will be recorded from the signing of informed consent through the follow-up visit (ie, 8 weeks after the last dose of study drug). Adverse events will be recorded from day 1 (ie, administration of study drug) until 4 weeks after the last dose of study drug.

CCI [REDACTED]

CCI [REDACTED]

<sup>1</sup> If a subject presents at a site for an unscheduled visit with symptoms related to increased disease activity, subjects should be evaluated for non-response or treatment failure criteria. If a subject meets non-response criteria during the eye examination, all activities listed in the ET visit (week 52) must be completed within 2 weeks. Subjects who meet treatment failure criteria during the eye examination may receive rescue medications at the investigator's discretion. If the rescue medication is a biologic, the subject must discontinue study drug and all activities listed in the ET visit (week 52) must be completed within 2 weeks. If the rescue medication is a non-biologic, the subject can continue on study and continue receiving study drug.

<sup>m</sup> For subjects who meet treatment failure criteria and require rescue medication that is a non-biologic, assessments as outlined in the Schedule of Activities should be followed, with the exception of efficacy assessments. Only efficacy assessments of BCVA and VFQ-25 will be completed at weeks 24 and 52, and no other efficacy assessments will be completed.

<sup>n</sup> Hepatitis B surface antigen and hepatitis C virus will be conducted. A positive result for the HBsAg will be exclusionary. Samples negative for HBsAg will be tested for HBsAb and HBcAb. If test results are positive for HBcAb or HBsAb, then HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

<sup>o</sup> QuantiFERON test or PPD test for TB will be performed. Note: T-SPOT<sup>®</sup> testing may be allowed after consultation with medical monitor.

Thyroid function tests include thyroid-stimulating hormone, free triiodothyronine and free thyroxine blood.

<sup>p</sup> Serum pregnancy test required for screening and urine pregnancy test required at all other times for WOCBP.

CCI [REDACTED]

<sup>s</sup> Subjects will be monitored at the study-site for at least 1 hour after the first 2 dose administrations of study drug. After week 4, subjects may perform home dosing of study drug at weeks without study visits (see footnote “a”) and do not need to return to the clinical site on those weeks. Subjects may begin self-administration of study drug from week 5. Subjects will be trained on study drug handling and self-administration of study drug at the study visits prior to beginning self-administration. Subject’s caregiver or designee can also be trained on home dosing based on subject’s preference. Study-site staff will administer study drug at the first 2 visits. Thereafter, if home dosing is a consideration, the subject or subject's caregiver or designee must administer and demonstrate competency for at least 2 visits prior to being allowed to dose at home. Otherwise, the subject will need to return to the site for all injections.

<sup>t</sup> A dosing diary will be completed for every home dosing administration.

<sup>u</sup> All subjects will receive a standardized prednisone/prednisolone burst of 60 mg/day at day 1 (week 0). By week 2 (day 14), subjects must undergo a protocol-defined oral steroid taper schedule which will decrease their dosage until they are off oral prednisone/prednisolone by week 15. Subjects who enter the study on topical corticosteroids (eye drops) will undergo a standardized taper schedule beginning on week 1 until all subjects are off topical steroids by week 10.

## 2. Introduction

Izokibep is a potent and selective inhibitor of interleukin (IL)-17A that is being developed for treatment of uveitis.

### 2.1. Study Rationale

Izokibep is a small protein molecule that acts as a selective, potent inhibitor of IL-17A, to which it binds with high affinity. Izokibep has been investigated in non-clinical and clinical studies including healthy volunteers and patients with psoriasis and psoriatic arthritis and is currently being studied in uveitis, psoriatic arthritis, axial spondyloarthritis and hidradenitis suppurativa. The current Phase 2b pivotal, double-blind, randomized, placebo-controlled dose-finding study will evaluate the efficacy, safety and immunogenicity of izokibep administered subcutaneously (SC) in adult subjects with active non-infectious, intermediate-, posterior- or pan-uveitis.

### 2.2. Background

#### 2.2.1. Disease Background

Uveitis results from a heterogeneous collection of disorders with diverse etiologies and pathogenic mechanisms ([Prete et al, 2016](#)). Uveitis can be classified, according to the primary anatomical location of the inflammation, into anterior and non-anterior uveitis.

Non-anterior uveitis can be further classified into intermediate-, posterior- or pan-uveitis (affecting more than 1 eye segment). Symptoms include severe intraocular inflammation, vision impairment with blurred or cloudy vision, floaters-spots in the eye and eye pain.

Infectious uveitis can be caused by bacterial and spirochetal diseases, viral diseases, fungal and parasitic infections ([Lin, 2015](#)). Non-infectious uveitis can be associated with systemic immune-mediated diseases such as spondyloarthritis (ie, ankylosing spondylitis and reactive arthritis), psoriatic arthritis and inflammatory bowel disease (IBD) ([Rosenbaum, 2015](#)), multiple sclerosis and Behçet's disease ([Chi et al, 2008](#)). Non-infectious uveitis can also occur without extraocular involvement ([Rosenbaum et al, 2019](#)).

The prevalence of non-infectious uveitis in the United States (US) was estimated to be 121/100,000 people based on administrative claims from 14 million privately insured individuals. Anterior non-infectious uveitis made up 81% (prevalence of 98/100,000 adults) versus 0.9% (prevalence of 1/100,000), 8.6% (prevalence of 10/100,000) and 9.6% (12/100,000) for non-infectious intermediate-, posterior- and pan-uveitis, respectively ([Thorne et al, 2016](#)). In Europe, up to 26% of total uveitis cases are intermediate-, posterior- or pan-uveitis ([Wakefield and Chang, 2005](#)).

Patients affected by uveitis are at risk of developing permanent visual impairment and blindness affecting 1 or both eyes. Cystoid macular edema was identified as the leading cause of visual impairment (41%) and blindness (29%) in patients with uveitis. Other eyesight-threatening complications include cataract and glaucoma ([Durrani et al, 2004](#)). All anatomical sites of inflammation of uveitis have the potential to lead to visual impairment and blindness, but the risk of visual impairment and blindness is highest in patients with posterior- or pan-uveitis

([Rothova et al, 1996](#)). Furthermore, patients with non-infectious, intermediate-, posterior- or pan-uveitis have a worse prognosis compared to those with anterior uveitis ([Wakefield and Chang, 2005](#); [Barisani-Asenbauer et al, 2012](#)).

Uveitis is a rare disease; nevertheless, it is the fourth most common cause of blindness among the working-age population in the developed world ([Barisani-Asenbauer et al, 2012](#)). In the US and other Western countries, it is estimated that approximately 10% to 20% of preventable blindness is caused by non-infectious, intermediate-, posterior- or pan-uveitis and associated complications ([Rothova et al, 1996](#); [Rothova et al, 1996](#); [Miserocchi et al, 2013](#); [Nguyen et al, 2011](#); [Gritz and Wong, 2004](#)). ; [Miserocchi et al, 2013](#); [Nguyen et al, 2011](#); [Gritz and Wong, 2004](#)).

Accordingly, if left untreated, uveitis carries a very high risk of progression to severe visual impairment, with a substantial impact on day-to-day functioning and overall quality of life. Vision loss due to non-infectious, intermediate-, posterior- or pan-uveitis can negatively affect patients' mental and physical health ([Schiffman et al, 2001](#); [Murphy et al, 2005](#); [Miserocchi et al, 2010](#)). Disability associated with visual impairment also can adversely affect patients' ability to work and may lead to absenteeism or early exit from the workforce.

Topical and systemic corticosteroids remain the cornerstone of treatment in patients with uveitis. Patients may require persistent high-dose systemic corticosteroids, high-dose systemic corticosteroids bursts or rapid systemic corticosteroids dose escalation. Conventional non-biologic systemic immunosuppressant therapies (eg, antimetabolites and alkylating agents) are mostly older, not well tolerated, and their efficacy has usually not been well-evidenced; presumably, at least one-third of patients still fail to achieve therapeutic remission with such agents.

The tumor necrosis factor-alpha (TNF- $\alpha$ ) inhibitor adalimumab is the only approved biologic for the treatment of uveitis. In the US, adalimumab is indicated for the treatment of adult patients with non-infectious intermediate-, posterior- and pan-uveitis ([Humira United States Prescribing Information FDA](#)[Humira United States Prescribing Information](#)). In Europe, adalimumab is indicated for the treatment of adult patients with non-infectious intermediate-, posterior- and pan-uveitis who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing or in whom corticosteroid treatment is inappropriate ([Humira SmPC EMA](#)).

### **2.2.2. Interleukin-17**

The immunopathology of uveitis is thought to be driven by autoreactive T cells targeting ocular tissues and acting in concert with cells of the innate immune system ([Lee and Dick, 2012](#)). Interleukin-17A, which is produced by T-helper (Th) 17 and other immune cells, is one of the major proinflammatory cytokines that contributes to the pathogenesis of several inflammatory disorders ([Miossec and Kolls, 2012](#)). Circulating Th17 cell levels are elevated during active uveitis and reduced following effective treatment ([Amadi-Obi et al, 2007](#)). Under normal conditions, circulating IL-17A levels are extremely low or undetectable, but in patients with active uveitis associated with systemic immune disorders such as Behçet's disease, increased serum and ocular IL-17A concentrations are seen ([Chi et al, 2008](#)). Moreover, IL-17A is produced in experimental models of T-cell-mediated uveitis and blocking IL-17A reduces ocular inflammation in these models ([Amadi-Obi et al, 2007](#); [Zhang et al, 2009](#)). These clinical and

experimental observations suggest that IL-17A may be an attractive therapeutic target in patients with non-infectious uveitis.

The efficacy of secukinumab, a human monoclonal antibody against IL-17, was evaluated in a Phase 3 SHIELD study for the treatment of chronic non-infectious uveitis ([Dick et al, 2013](#)). However, secukinumab administered at SC doses of 150 or 300 mg every 2 or 4 weeks did not meet primary efficacy endpoints of reduction of uveitis occurrence or vitreous haze score during withdrawal of concomitant immunosuppressive medication. The secondary efficacy data from the study suggest a beneficial effect of secukinumab in reducing the use of concomitant immunosuppressive medications ([Dick et al, 2013](#)). These findings raised the possibility that insufficient exposure to secukinumab may have led to the study not meeting its primary endpoint.

The importance of adequate exposures was demonstrated in a small dose-ranging Phase 2 study with secukinumab intravenous (IV) or SC in patients with active non-infectious intermediate, posterior- or pan-uveitis who required corticosteroid-sparing immunosuppressive therapy. In this study, 37 patients were randomized to secukinumab 300 mg SC every 2 weeks (Q2W) for 4 doses, secukinumab 10 mg/kg IV Q2W for 4 doses or secukinumab 30 mg/kg IV every 4 weeks for 2 doses. Secukinumab IV doses (30 mg/kg IV and 10 mg/kg IV) produced higher responder rates at 72.7% and 61.5% versus the 33.3% response rate seen with secukinumab 300 mg SC Q2W dosing. Other measures, including time to response onset, change in visual acuity and change in vitreous haze score, showed numeric trends favoring IV dosing ([Letko et al, 2015](#)). As discussed later in this document, the izokibep CCI once weekly (QW) SC dose has very similar exposure level to the secukinumab 10 mg/kg IV dose.

### 2.2.3. Izokibep Background

Izokibep is a biologic drug that binds IL-17A with high affinity and with a potency corresponding to clinically tested monoclonal in terms of blocking the biological activity of IL-17A. Izokibep has the potential to be an efficacious treatment for a variety of IL-17A-related diseases. The smaller size of izokibep compared to monoclonal antibodies offers advantages in terms of required dosing volumes and potential for alternative pharmacological formulations.

Izokibep is based on a small protein binding to and blocking the biological effect of the cytokine IL-17A. The izokibep protein molecule also contains CCI

IL-17 inhibitors have already demonstrated efficacy and a favorable safety profile in different inflammatory diseases, including psoriasis, psoriatic arthritis and axial spondyloarthritis. These include secukinumab (Cosentyx®) and ixekizumab (Taltz®) in the US, Canada and the EU.

A detailed description of the chemistry, pharmacology, pharmacokinetics (PK), efficacy and safety of izokibep is provided in the [Investigator's Brochure](#).

### 2.2.3.1. Non-clinical studies

Assessments of target-binding specificity have demonstrated high specificity and affinity of izokibep to IL-17A and to albumin. The *in vitro* and *in vivo* pharmacodynamic evaluations show that izokibep has a 3- to 5-fold higher potency than the anti-IL-17A monoclonal antibody secukinumab on a molar basis and appears to be approximately equipotent to ixekizumab on a molar basis.

Pharmacokinetic data for IV- and SC-administered izokibep have been obtained in rat and monkey. Pharmacokinetic assessments in rat and monkey indicate that the time course of izokibep concentrations after a bolus IV injection and SC injection is well described by a 2- or 3-compartment model. Pharmacokinetic assessments indicate that the elimination rate of izokibep is similar to that of albumin in the respective species.

Repeated (10 days to 3 months) SC or IV administration of izokibep to cynomolgus monkeys was well tolerated with no observed adverse effect levels (NOAELs) of 40 mg/kg/dose administered every third day (IV, 28-day study) and 20 mg/dose administered every third day (SC, 28-day) and 20 mg/kg/week (SC, 3-month study), being the highest dose levels tested in the respective studies.

In the 26-week repeated dose toxicity study in cynomolgus monkeys, weekly SC injection of 10, 20 or 40 mg/kg/week izokibep to monkeys for 26 weeks was generally well tolerated. However, due to the presence of local abscessation and systemic sequelae in 1 female administered 40 mg/kg/week, which was considered adverse, the NOAEL for SC administration was considered to be 20 mg/kg/week.

In the enhanced pre- and post-natal developmental toxicity study in cynomolgus monkeys, SC izokibep administration of up to 40 mg/kg/week to pregnant monkeys for approximately 21 weeks was well tolerated. The NOAEL was 40 mg/kg/week.

Izokibep has been shown to enter healthy cynomolgus monkeys' eyes in a dose-dependent manner that parallels systemic exposures of izokibep when delivered via inhalation.

The results from the immunotoxicity screening assays do not suggest that izokibep has an intrinsic capacity for immune system activation.

Metabolism and genotoxicity have not been investigated, since izokibep is a protein molecule and contains only naturally occurring amino acids.

For additional information, please refer to the [Investigator's Brochure](#).

### 2.2.3.2. Clinical Overview

A first-in-human multipart clinical study (Study ABY-035-001, EudraCT number 2015-004531-13, CCI [REDACTED]) has been conducted with the parenteral formulation of izokibep. Izokibep was administered IV and SC to healthy subjects and plaque psoriasis patients, in doses ranging from CCI [REDACTED] in a single or multiple dose regimen.

A Phase 2 dose-finding study in subjects with moderate to severe plaque psoriasis recently completed the core part (1-year) and is currently ongoing for further treatment up to 3 years (Study ABY-035-002, EudraCT number 2017-001615-36, CCI [REDACTED]). One hundred eight subjects were randomized into CCI [REDACTED] izokibep or placebo.

The treatment period consisted of an induction period (12 weeks), an optimization period (12 weeks) and an individualization period (24 weeks). The induction period was double-blind and placebo-controlled.

The primary endpoint of the study was the proportion of patients that achieved a Psoriasis Area and Severity Index response of 90% (PASI90) after 12 weeks of treatment. PASI90 at 12 weeks was 71.4% and 59.1% in subjects treated with CCI and CCI Q2W of izokibep, respectively. In the lower dose groups, CCI izokibep, only 5.0% and 19.0% of subjects, respectively, reached the primary endpoint. None of the subjects receiving placebo reached PASI90 response at week 12. At week 24, PASI90 responses were comparable between the initial CCI treatment groups. The safety and efficacy data obtained from the 52-week core period of the study with izokibep suggest a favorable benefit-risk profile in plaque psoriasis ([Investigator's Brochure](#)).

The results from a dose-ranging Phase 2 study comparing secukinumab dosed IV versus SC suggest that higher exposures may be necessary to achieve adequate therapeutic concentrations in this patient population ([Letko et al, 2015](#)). As reviewed below, there are no dose-limiting AEs for izokibep moving from the CCI SC dosing, which support the testing of the CCI QW and CCI Q2W dosing.

### 2.2.3.3. Safety Overview

In the first-in-human study in healthy subjects and subjects with psoriasis (Study ABY-035-001), doses of up to CCI IV and SC of izokibep (n = 62) were well tolerated, with no deaths or treatment-related serious AEs (SAEs).

Intravenous administration (single doses up to CCI in 46 subjects in total) resulted in the following treatment-emergent AEs (TEAEs) by preferred term: oropharyngeal pain (10.9%), nasopharyngitis (6.5%), diarrhea (4.3%) and headache (4.3%). A further 9 TEAEs were reported, and affected 1 subject each (2.2% each). Subcutaneous administration (single and multiples doses up to CCI in 21 subjects in total) resulted in the following TEAEs by preferred term: injection site reaction (61.9%) and injection site pain (28.6%). A further 11 TEAEs were reported, and affected 1 subject each (5.2% each). The majority of the injection site reactions were of mild intensity and required no treatment or limited therapy.

In the Phase 2, 52-week core period in subjects with plaque psoriasis (ABY-035-002), multiple doses of up to CCI SC of izokibep (n = 108) were well tolerated with no deaths or treatment-related SAE. A total of 65 subjects (60.2%) experienced at least 1 izokibep-related TEAE. The most common izokibep-related TEAEs (n/%) were injection site reaction (42/38.9%), nasopharyngitis (13/12%), diarrhea (7/6.5%) and fatigue (6/5.6%) consistent with the first-in-human study.

For more details on the safety and tolerability of izokibep, refer to the [Investigator's Brochure](#).

### 2.2.3.4. Pharmacokinetics

Following SC administration of single izokibep doses in the first-in-human study (Study ABY-035-001), median time to maximum observed concentration ( $t_{max}$ ) was 60 hours post-dose. After reaching maximum observed plasma concentration ( $C_{max}$ ), plasma levels of izokibep declined in an apparent mono- or bi-phasic manner with the geometric mean  $t_{1/2}$  being

278 hours which was similar to that after IV administration (288 hours). Individual  $t_{1/2}$  estimates ranged from 199 to 464 hours and 220 to 340 hours for SC and IV treatments, respectively. The absolute bioavailability after a CCI dose of izokibep was estimated to 77%. In general, as assessed by the geometric percent coefficient of variation (CV%) low between-subject variability was noted for area under the concentration-time curve (AUC) extrapolated to infinity ( $AUC_{0-\infty}$ ) and  $C_{max}$  for both dose routes, with values ranging from 20% to 22% and 14% to 15%, respectively.

Following CCI repeated SC doses, maximum plasma concentrations occurred at a median  $t_{max}$  of 48.0 hours post-dose on days 1 and 29 (individual range: 24.0 to 71.0 hours post-dose). On day 85, median  $t_{max}$  was slightly later at 71.6 hours post-dose (individual range: 66.6 to 73.1 hours post-dose). After reaching  $C_{max}$  on day 85, plasma concentrations of izokibep declined in an apparent mono- or bi-phasic manner with a geometric mean  $t_{1/2}$  of 279 hours with individual patients ranging from 229 to 423 hours. Pre-dose trough izokibep plasma concentrations showed that steady state was achieved by day 71, following C doses of izokibep administered Q2W. There was evidence of accumulation following repeated dosing by day 85 with geometric mean accumulation ratio, based on AUC over the dose interval ( $AUC_{0-\tau}$ ) of 1.95, and individual patients ranging from 1.35 to 5.09. Between-patient variability, based on geometric CV%, was moderate on the monitored study days for  $AUC_{0-\tau}$  with values ranging from 29.4% to 36.0%, and low to moderate for  $C_{max}$  with values ranging from 20.4% to 28.8%.

For more details on the PK of izokibep, refer to the [Investigator's Brochure](#).

## 2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of izokibep may be found in the [Investigator's Brochure](#).

### 2.3.1. Risk Assessment

Izokibep is a biologic drug that binds IL-17A with high affinity and with a potency corresponding to clinically tested monoclonal antibodies in terms of blocking the biological activity of IL-17A.

- IL-17A inhibitors, including secukinumab and ixekizumab as well as izokibep, do not appear to have dose-limiting AEs.
- Class effects and potential risks seen with other IL-17 inhibitors have not been identified with izokibep. Given the small numbers of subjects treated to date, class effects and potential risks of IL-17 inhibitors will be explicitly monitored (ie, events of special interest) and have been taken into consideration in the development of inclusion and exclusion criteria. These events include candida infections, IBD, suicidal ideation, malignancies, major cardiovascular and cerebrovascular events, TB, opportunistic infections and serious infections.

- No genotoxicity or carcinogenicity is foreseen as izokibep is a protein consisting of natural amino acids. However, since no data are available at this stage of clinical development on possible effects on the reproductive system, the following precautionary measure will be taken:
  - Females of childbearing potential as well as reproductive female partners of male patients must use an adequate method of contraception while participating in the clinical study until 8 weeks after the last dose of study drug. Pregnancy testing will be performed at regular intervals prior to, during treatment and after the end of treatment.

### 2.3.2. Benefit Assessment

There is an unmet medical need for the treatment of non-infectious, intermediate-, posterior- or pan-uveitis and this represents the focus of the izokibep development plan. These types of uveitis are at a higher risk for vision loss compared to anterior uveitis. Disease management often requires chronic corticosteroid use, whether in an oral or injectable form, that presents with predictable long-term side effects, whereas in general, anterior uveitis may be managed with topical corticosteroids.

Immunosuppressive agents have been used as corticosteroid-sparing or additive therapy in non-infectious, intermediate-, posterior- or pan-uveitis, although there is a lack of robust clinical evidence to support their use. These immunosuppressive agents are not effective in all patients and carry risks of known adverse effects.

The TNF- $\alpha$  inhibitor adalimumab is the only approved biologic for the treatment of uveitis. Nevertheless, a large proportion of patients are also refractory to these treatments and can experience reduction of vision.

The potential benefit of the study is that it will establish if treatment with izokibep improves the time to treatment failure compared to placebo in subjects with active non-infectious intermediate-, posterior- or pan-uveitis despite systemic corticosteroid therapy. The objective is to determine whether izokibep is effective in controlling uveitis while also allowing for the discontinuation of systemic corticosteroids. Subjects will be allowed to continue 1 pre-study immunosuppressant throughout the study.

Given the known possibility of progression to severe visual impairment if uveitis goes untreated, subjects across all treatment arms of this study will be initiated on high-dose systemic corticosteroids which will be tapered over the first 15 weeks of the study, per protocol. The use of concomitant background steroids mitigates the risk of progression of disease in the placebo group, justifying a placebo cohort. Expected time to treatment failure in the placebo and corticosteroid arm is informed by results seen in a similarly designed Phase 3 interventional study of adalimumab in active non-infectious uveitis, where subjects in both arms were given bursts of high-dose systemic corticosteroids, tapered over 15 weeks. In the adalimumab study, time to treatment failure in the placebo group was 13 weeks ([Jaffe et al, 2016](#)).

Based on the safety, efficacy and PK data obtained in clinical studies with izokibep in healthy subjects and in patients with psoriasis, a favorable benefit-risk profile in uveitis is suggested. Based on published data showing efficacy and safety for other IL-17 inhibitors in other inflammatory disease and in proof-of-concept studies in patients with non-infectious,

intermediate-, posterior- or pan-uveitis, the benefit-risk relationship in patients with uveitis also appears favorable and justifies clinical development of izokibep in uveitis as well. Due to its small molecular size as compared to monoclonal antibodies and its binding to albumin, izokibep may have the potential to better reach inflamed tissues and may provide higher exposure relative to monoclonal antibodies.

The investigator is referred to the current Investigator's Brochure where additional and more detailed information (including non-clinical toxicology, metabolism, pharmacology and safety experience) regarding potential risks and benefits of izokibep can be found.

### **2.3.3. Overall Benefit-Risk Conclusion**

The following considerations are important for the benefit-risk assessment:

- Only subjects with active non-infectious, intermediate-, posterior- or pan-uveitis in at least 1 eye despite at least 2 weeks of prednisone/prednisolone (7.5 mg/day to 40 mg/day) or corticosteroid equivalent will be enrolled.
- The inclusion and exclusion criteria will ensure that subjects who might be predisposed to a higher risk of drug-related TEAEs are either excluded or identified and treated with caution. Class effects seen with other IL-17 inhibitors have been taken into account when designing the eligibility criteria. Subjects with active infections and with a history of autoimmune, chronic inflammatory or connective tissue disease will be excluded from participating in the study.
- Subjects will be monitored at the study-site for at least 1 hour after the first 2 dose administrations of izokibep.
- Participation in the study is voluntary. Each subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

Taking into account the measures taken to minimize risk to subjects participating in this study, the lack of clear dose-limiting AEs associated with izokibep, and the pre-existing data on the effects of IL-17 inhibitors in non-infectious, intermediate-, posterior- or pan-uveitis, the potential risks identified in association with izokibep are justified by the anticipated benefits that may be afforded to subjects with uveitis.

### **2.3.4. COVID-19 Benefit/Risk Assessment**

A benefit-risk assessment related to severe acute respiratory syndrome coronavirus (SARS-CoV-2) has been considered for this study and concluded that the coronavirus disease of 2019 (COVID-19) pandemic does not alter the overall benefit-risk for conducting this study. Risk mitigation measures will be implemented based on the prevailing situation during study conduct, at the investigator's discretion and in accordance with local and institutional guidelines as applicable. The benefit-risk of the study in relation to the COVID-19 pandemic will continue to be assessed during the study and additional or revised measures may be implemented based on any updates to the benefit-risk assessment.

### 3. Objectives, Endpoints and Estimands

| Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Endpoints                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                            |
| <ul style="list-style-type: none"> <li>To demonstrate that izokibep is efficacious compared to placebo, as measured by time to treatment failure occurring up to week 52</li> </ul>                                                                                                                                                                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>Time to treatment failure</li> </ul>                                                                                                |
| <b>Secondary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                            |
| <p>To demonstrate that izokibep is efficacious, as measured by:</p> <ul style="list-style-type: none"> <li>Change in BCVA from best state achieved before week 10 to week 24</li> <li>Change in the NEI-VFQ-25 score from best state achieved before week 10 to week 24</li> <li>Change in central retinal thickness (by SD-OCT) from baseline to week 10</li> <li>Change in central retinal thickness (by SD-OCT) from best state achieved <math>\leq</math> week 10 up to week 52</li> <li>Proportion of subjects that achieve quiescence at week 10</li> </ul> | <ul style="list-style-type: none"> <li>BCVA</li> <li>NEI-VFQ-25 score</li> <li>Central retinal thickness</li> <li>Central retinal thickness</li> <li>Quiescence</li> </ul> |
| <p>To assess the safety and tolerability of izokibep as measured by the incidence of TEAEs, events of special interest, SAEs and clinically significant laboratory values and vital signs</p>                                                                                                                                                                                                                                                                                                                                                                     | <ul style="list-style-type: none"> <li>TEAEs, events of special interest and SAEs</li> <li>Laboratory values and vital signs at collected timepoints</li> </ul>            |
| <b>CCI</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                            |
| <p><b>CCI</b></p> <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li></li> </ul> </li> <li> <ul style="list-style-type: none"> <li></li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                            | <p><b>C</b></p>                                                                                                                                                            |

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ACC = anterior chamber cell; CCI = [REDACTED]; BCVA = best corrected visual acuity; CST = central subfield thickness; CCI = [REDACTED]; IL = interleukin; NEI = National Eye Institute; PRO = patient-reported outcome; SAE = serious adverse event; [REDACTED]; CCI = [REDACTED]; SUN = Standardization of Uveitis Nomenclature; TEAE = treatment-emergent adverse event; TNF = tumor necrosis factor; VFQ-25 = Visual Function Questionnaire-25

## Endpoint Definitions

### Treatment Failure

| Endpoint/Parameter                                                       | Non-response                                                                                                                                                         | Treatment Failure                                                                                                                      |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
|                                                                          | At any visit from week 4 up to but not including week 10, a subject is defined as a non-responder by meeting at least 1 of the following criteria in at least 1 eye: | At or after week 10, a subject is defined as reaching treatment failure by meeting $\geq 1$ of the 4 criteria below in at least 1 eye: |
| Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions | New active, inflammatory lesions, or worsening of previously identified inflammatory lesions, relative to baseline                                                   | New active, inflammatory lesions, or worsening of previously identified inflammatory lesions, relative to baseline                     |
| ACC count (SUN Grade)                                                    | $\geq 1$ -grade increase (worsening) from baseline                                                                                                                   | 2-step increase relative to the best state achieved up to week 10 <sup>a</sup>                                                         |
| Vitreous haze (NEI/SUN Grade)                                            | $\geq 1$ -grade increase (worsening) from baseline                                                                                                                   | 2-step increase relative to the best state achieved up to week 10 <sup>a</sup>                                                         |
| Visual acuity (ETDRS)                                                    | Worsening of BCVA by $\geq 15$ letters relative to the best state achieved                                                                                           | Worsening of BCVA by $\geq 15$ letters relative to the best state achieved up to week 10                                               |

ACC = anterior chamber cell; BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI = National Eye Institute; SUN = Standardization of Uveitis Nomenclature

<sup>a</sup> A 2-step increase is represented by a change of Grade 0 to Grade 2+ or Grade 0.5+ to Grade 3+.

### Quiescence

| Quiescence (both eyes)                                                   |                             |
|--------------------------------------------------------------------------|-----------------------------|
| Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions | No new inflammatory lesions |
| ACC Count (SUN Grade)                                                    | Trace or absent (0.5+ or 0) |
| Vitreous Haze (NEI/SUN Grade)                                            | Trace or absent (0.5+ or 0) |

ACC = anterior chamber cell; NEI = National Eye Institute; SUN = Standardization of Uveitis Nomenclature

## Primary Estimand

Please refer to [Section 9.3.2](#).

## Secondary Estimand(s)

Please refer to [Section 9.3.3](#).

## 4. Study Design

### 4.1. Overall Design

This is a Phase 2b pivotal multi-center, dose-finding, randomized, double-blind, placebo-controlled study. The plan is to investigate the efficacy, safety and immunogenicity of izokibep in subjects with active non-infectious, intermediate-, posterior- or pan-uveitis in at least 1 eye despite treatment with at least 2 weeks of prednisone/prednisolone 7.5 mg/day to 40 mg/day inclusive (or corticosteroid equivalent). Subjects may continue treatment with 1 non-biologic (non-corticosteroid) immunosuppressive therapy as long as the dose has been stable for  $\geq 4$  weeks prior to day 1.

Approximately 100 subjects with active non-infectious, intermediate-, posterior- or pan-uveitis despite at least 2 weeks of prednisone/prednisolone 7.5 mg/day to 40 mg/day (or corticosteroid equivalent) will be enrolled. The study consists of up to a 28-day (4 weeks) screening period, a 51-week treatment period and a follow-up period with visits at 8 weeks and 14 weeks after the last dose of study drug to assess safety and immunogenicity.

Eligible subjects will be randomized into 1 of 2 groups in a **CC** ratio as follows:

- Group 1: placebo SC QW
- Group 2: izokibep SC **CCI** QW

Of the approximately 100 subjects to be enrolled, approximately 20 are attributed to those enrolled under previous versions of the protocol (ie, previously included Q2W arm), with an additional approximately 80 subjects (40/arm) to be enrolled in the QW arms.

The first dose of study drug (ie, izokibep or placebo) will be administered on day 1 (week 0).

Randomization will be stratified by any prior treatment with a systemic TNF- $\alpha$  inhibitor (yes/no) and concomitant systemic inflammatory disease (yes/no).

All subjects will receive a standardized prednisone/prednisolone burst of 60 mg/day from day 1 up to day 14 (week 0 to week 1). By week 2, subjects will undergo a protocol-defined mandatory taper schedule which will decrease their dosage until they are off oral prednisone/prednisolone by week 15 (see [Section 6.1.2](#)). Subjects who enter the study on topical corticosteroids (eye drops) will undergo a standardized taper schedule beginning at week 1 until all subjects have completely discontinued topical corticosteroids no later than week 10 ([Section 6.8.2](#)).

Subjects will complete study assessments according to the study visits outlined in the SoA ([Section 1.3](#)). From week 4 up to but not including week 10, subjects will be assessed for non-response ([Section 3](#)). At or after week 10, subjects will be assessed for treatment failure as described in [Section 3](#). Subjects who meet the criteria for non-response must complete the early termination visit (week 52) within 2 weeks. Subjects who meet treatment failure criteria may receive rescue medications at the investigator's discretion. If the rescue medication is a biologic, the subject must discontinue study drug and must complete the early termination visit (week 52) within 2 weeks. If the rescue medication is a non-biologic, the subject can continue on study and continue receiving study drug. Assessments as outlined in the SoA ([Section 1.3](#)) should be followed, with the exception of efficacy assessments. Only efficacy assessments of best

corrected visual acuity (BCVA) and VFQ-25 will be completed at weeks 24 and 52, and no other efficacy assessments will be completed. Refer to [Section 7.1](#) for discontinuation of study drug.

Both of the subject's eyes should be evaluated for the purpose of determining eligibility based on inclusion and exclusion criteria, and for the purpose of assessing treatment failure ([Section 3](#)). There will be no designated "study eye".

Subjects assigned to receive placebo or active, administered QW, will be randomized in a **1:1** ratio. Study drug doses are fixed and will not be adjusted for individual subjects during the study.

The last dose of study drug will be administered at week 51. Analysis of the primary efficacy endpoint will occur after all subjects have had the opportunity to complete the week 24 visit or terminate early from the study.

#### **4.1.1. Independent Data Monitoring Committee**

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

The DMC will consist of at least 1 medical expert with the relevant therapeutic area expertise and at least 1 statistician and will have a minimum of 3 members, 1 of whom will serve as the Chair. The DMC responsibilities, members (including their qualifications and possible conflicts of interest), authorities, meeting frequency to review unblinded interim data, and procedure will be documented in the DMC charter. The committee will meet as needed as outlined in the DMC charter. After each review, the DMC will make recommendations regarding the continuation of the study based on safety. The DMC may review unblinded efficacy data when all subjects have had the opportunity to complete the week 10 visit. The DMC may make a recommendation on further development activities for izokibep based on this data review.

The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The study team operationalizing the day-to-day of the study, the subjects and the investigators will remain blinded to these interim results until after the study is completed. The committee will meet as needed as outlined in the DMC charter.

#### **4.1.2. Number of Sites**

Approximately 60 sites across North America and Europe will participate in this study. Additional sites and regions may be added. Sites that do not screen subjects within 2 months of site initiation may be closed.

#### **4.1.3. Number of Subjects**

Participants in this clinical investigation shall be referred to as "subjects". Approximately 100 subjects will be enrolled/randomized. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

#### 4.1.4. Study Duration for Subjects

The maximum planned length of participation in the study for an individual subject is up to 69 weeks, which includes the following:

- Screening period of up to 28 days (4 weeks)
- 51-week treatment period
- Follow-up visit at 8 weeks and 14 weeks after the last dose of study drug

#### 4.1.5. Scientific Rationale for Study Design

The design of this clinical study was chosen to evaluate izokibep in subjects with active non-infectious, intermediate-, posterior- or pan-uveitis in at least 1 eye. The primary aim of the study is to provide approximately 1-year placebo-controlled data demonstrating the safety and efficacy of izokibep administered SC at a dose of CCI QW for the treatment of active non-infectious, intermediate-, posterior- or pan-uveitis. The primary endpoint of time to treatment failures will be evaluated after all subjects have the opportunity to complete the week 24 study visit. Long-term efficacy beyond week 24 will be explored up to week 52 and safety will be explored up to the end of study.

Standard statistical procedures will be utilized in this study. Efficacy measurements in this study have been selected or designed to assess disease activity in subjects with non-infectious, intermediate-, posterior- or pan-uveitis. All clinical and laboratory procedures in this study are standard and generally accepted.

Males and females  $\geq 18$  years and  $\leq 75$  years with active non-infectious, intermediate-, posterior- or pan-uveitis in at least 1 eye despite treatment with at least 2 weeks of prednisone/prednisolone 7.5 mg/day to 40 mg/day, inclusive (or corticosteroid equivalent), who meet all inclusion criteria and who do not meet any of the exclusion criteria are eligible for this study. The population being studied represents a population normally seen in clinical practice. This ensures the activity of izokibep can be evaluated across a distribution of disease severity in the study.

#### 4.2. Justification for Dose

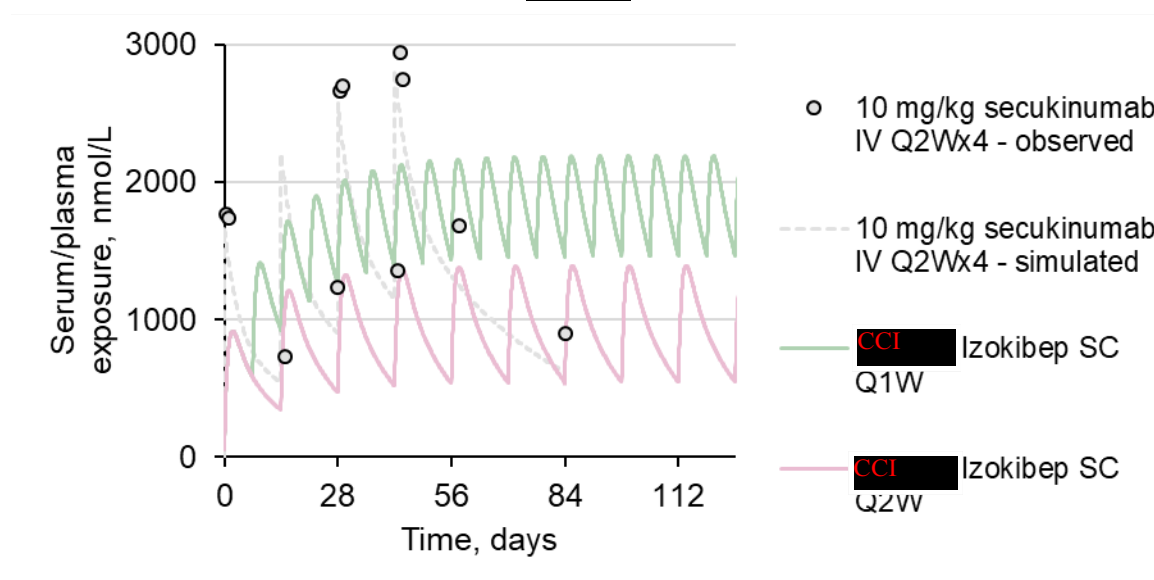
The dose of izokibep is CCI SC QW administered from day 1 (week 0) through week 51 in subjects randomized to izokibep.

The selection of the dosing regimen is informed by the following facts. In the clinical setting, izokibep has not demonstrated dose-limiting safety/tolerability up to CCI Q2W with multiple doses. A dose of CCI QW has 10-fold margin for  $C_{\max}$  and 9-fold margin for  $AUC_{0-\tau}$  based on the NOAEL from non-clinical cynomolgus monkey toxicity studies (Table 1). Furthermore, IV administration of secukinumab at doses of 10 mg/kg (approximately 800 mg; Q2W on 4 occasions) or 30 mg/kg (2400 mg; Q4W on 2 occasions) in subjects with uveitis did not identify any dose-related safety/tolerability concerns (Letko et al, 2015). Finally, based on PK modeling of the izokibep and secukinumab plaque psoriasis data and the available data with secukinumab in uveitis, the sponsor aimed to approximate the observed exposure of 10 mg/kg secukinumab IV Q2W (administered on 4 occasions) with the CCI QW SC dose of izokibep as shown in Figure 1 and Table 2 (internal data to ACELYRIN).

**Table 1.  $C_{\max}$  and  $AUC_{0-\tau}$  at NOAEL in Cynomolgus Monkey Versus Predicted Exposure Levels in Man and Respective Margins**

| Parameter      | NOAEL (20 mg/kg/week)<br>in Cynomolgus Monkey | Predicted in Subjects<br>at Steady State CCI [REDACTED] QW) | Margin |
|----------------|-----------------------------------------------|-------------------------------------------------------------|--------|
| $C_{\max}$     | 409 $\mu\text{g/mL}$                          | 40.8 $\mu\text{g/mL}$                                       | 10     |
| $AUC_{0-\tau}$ | 52500 $\text{h}\cdot\mu\text{g/mL}$           | 5850 $\text{h}\cdot\mu\text{g/mL}$                          | 9.0    |

$AUC_{0-\tau}$  = area under the concentration-time curve over a dosing interval;  $C_{\max}$  = maximum observed plasma concentration; h = hour; NOAEL = no observed adverse effect level; QW = once a week

**Figure 1. Observed and Simulated PK Profiles for 10 mg/kg IV Q2W×4 Secukinumab Versus Simulated Profiles for CCI [REDACTED] Izokibep SC QW and Q2W**

IV = intravenous; PK = pharmacokinetic; QW/Q1W = once a week; Q2W = every 2 weeks; SC = subcutaneous

**Table 2. Predicted Exposure at Steady State for CCI [REDACTED] Izokibep SC QW**

| Parameter            | Unit                         | Value            | Unit                          | Value |
|----------------------|------------------------------|------------------|-------------------------------|-------|
| $C_{\max}$           | nmol/L                       | 2190             | $\mu\text{g/mL}$              | 40.8  |
| $C_{\min}$           | nmol/L                       | 1460             | $\mu\text{g/mL}$              | 27.2  |
| $C_{\text{average}}$ | nmol/L                       | 1870             | $\mu\text{g/mL}$              | 34.8  |
| $AUC_{0-\tau}$       | $\text{h}\cdot\text{nmol/L}$ | $31.5\cdot 10^4$ | $\text{h}\cdot\mu\text{g/mL}$ | 5850  |

$AUC_{0-\tau}$  = area under the concentration-time curve over the dose interval;  $C_{\text{average}}$  = average observed plasma concentration;  $C_{\max}$  = maximum observed plasma concentration;  $C_{\min}$  = minimum observed plasma concentration; QW = once a week; SC = subcutaneous

The dose of izokibep used in this study supports the maximum likelihood of demonstrating the potential efficacy for izokibep in subjects with non-infectious, intermediate-, posterior- or pan-uveitis within an acceptable safety profile. Measures have also been taken to ensure the

well-being of subjects by applying appropriate inclusion and exclusion criteria to recruit a broad population that is most likely to benefit from treatment, while excluding subjects with an unacceptable risk to enter the study ([Section 5](#)). Further, during the study, measures are in place to monitor the safety of subjects on a regular basis. An independent DMC will also review the data on an ongoing basis, as detailed in [Section 4.1.1](#).

### **4.3. End of Study Definition**

The primary completion for the study is the date the last subject has had the opportunity to complete the week 24 assessment for the purpose of the primary endpoint.

The end of the study is defined as the date of the last scheduled procedure including the last follow-up visit (ie, week 65) shown in the SoA ([Section 1.3](#)) for the last subject in the study globally.

A subject is considered to have completed the study if the subject has completed all periods of the study including the last scheduled procedure shown in the SoA ([Section 1.3](#); ie, week 65 follow-up visit).

## 5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

### 5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>General</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <ol style="list-style-type: none"> <li>1. Subject has provided signed informed consent including consenting to comply with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.</li> <li>2. Subject must be <math>\geq 18</math> (or the legal age of consent in the jurisdiction in which the study is taking place) and <math>\leq 75</math> years of age, at the time of signing the informed consent.</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Type of Subject and Disease Characteristics</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <ol style="list-style-type: none"> <li>3. Subject is diagnosed with non-infectious intermediate-, posterior- or pan-uveitis.</li> <li>4. Active disease defined by the presence of at least 1 of the following criteria in at least 1 eye despite treatment with stable doses of corticosteroids for at least 2 weeks prior to day 1:             <ul style="list-style-type: none"> <li>○ Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesion by dilated indirect ophthalmoscopy, fundus photography, fluorescein angiography (FA), and Spectral-Domain Optical Coherence Tomography (SD-OCT) to determine whether a lesion is active or inactive (the central reading center assessment using FA, fundus photography and/or SD-OCT is required to confirm eligibility prior to day 1).</li> <li>○ <math>\geq 2+</math> vitreous haze (National Eye Institute [NEI]/Standardization of Uveitis Nomenclature [SUN] criteria) by digital indirect ophthalmoscope and fundus photography (the central reading center assessment using fundus photography is required to confirm eligibility prior to day 1).</li> </ul> </li> <li>5. Currently receiving treatment with oral corticosteroids (<math>\geq 7.5</math> mg/day to <math>\leq 40</math> mg/day oral prednisone/prednisolone or corticosteroid equivalent) at a stable dose for at least 2 weeks prior to day 1.</li> </ol> |
| <b>Other Inclusions</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <ol style="list-style-type: none"> <li>6. No known history of active tuberculosis (TB).</li> <li>7. Subject has a negative TB test at screening, as defined by<sup>1</sup>:             <ul style="list-style-type: none"> <li>○ Negative QuantiFERON test OR</li> <li>○ Negative purified protein derivative (PPD) test (<math>&lt; 5</math> mm of induration at 48 to 72 hours after test is placed).</li> </ul> </li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

- Subjects with a positive PPD test and a history of Bacillus Calmette-Guerin vaccination will be allowed with a negative QuantiFERON test.
- Subjects with a positive or indeterminate QuantiFERON test are allowed if all of the following are satisfied:
  - No symptoms of TB as determined by investigator.
  - Documented history of adequate prophylaxis initiation prior to receiving first dose of study drug.
  - No known exposure to a case of active TB after most recent prophylaxis.
  - No evidence of active TB on chest radiograph within 3 months prior first dose of study drug.

<sup>1</sup> T-SPOT TB test may be used to establish eligibility if agreed upon with the medical monitor.

### **Sex and Contraceptive/Barrier Requirements**

#### **8. Male and female subjects:**

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

##### **a. Male subjects:**

Male subjects are eligible to participate if they agree to the following during the study drug period and for at least 8 weeks after the last dose of study drug:

- Refrain from donating fresh unwashed semen.

Plus either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

##### **b. Female subjects:**

- A female subject is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:
  - Is a woman of nonchildbearing potential as defined in [Section 10.4](#) (Contraceptive and Barrier Guidance)

OR

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>○ Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of &lt; 1%, as described in <a href="#">Section 10.4</a>, during the study drug period and for at least 8 weeks after the last dose of study drug. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study drug.</li> <li>• A WOCBP must have a negative highly sensitive serum pregnancy test at screening and negative urine pregnancy test on day 1 prior to the first dose of study drug; see <a href="#">Section 8.2.6.1</a>.</li> </ul> |
| <p><b>Prior Therapy</b></p> <p>9. Have demonstrated inadequate response to adalimumab, or for whom adalimumab is contraindicated.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

## 5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

| <b>Disease-related Medical Conditions</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> <li>1. Subject with isolated anterior uveitis</li> <li>2. Subject with serpiginous choroidopathy</li> <li>3. Subject with confirmed or suspected infectious uveitis, including but not limited to infectious uveitis due to TB, syphilis, cytomegalovirus, Lyme disease, toxoplasmosis, human T-lymphotropic virus type 1 infection, Whipple's disease, herpes zoster virus and HSV</li> <li>4. Subject with corneal or lens opacity that precludes visualization of the fundus or that likely requires cataract surgery during the duration of the study</li> <li>5. Planned (elective) eye surgery during the course of the study</li> <li>6. History of prior refractive laser surgery, laser surgery of the macula (including photodynamic therapy or focal laser photocoagulation), retinal laser photocoagulation, or neodymium-doped yttrium aluminum garnet posterior capsulotomy <math>\leq 30</math> days before day 1</li> <li>7. History of any other prior ocular surgery <math>\leq 3</math> months prior to day 1 except surgery for cosmetic reasons that is not expected to impact vision</li> <li>8. Subject with intraocular pressure of <math>\geq 25</math> mmHg while on <math>\geq 2</math> glaucoma medications or evidence of glaucomatous optic nerve injury</li> <li>9. Subject with severe vitreous haze that precludes visualization of the fundus prior to first dose of study drug</li> <li>10. Subject has a contraindication for mydriatic eye drops OR subject cannot be dilated sufficiently well to permit good fundus visualization</li> <li>11. Subject with BCVA &lt; 20 letters (Early Treatment Diabetic Retinopathy Study [ETDRS]) in at least 1 eye prior to first dose of study drug</li> </ol> |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| <p>12. Subject with proliferative or severe non-proliferative retinopathy or clinically significant macular edema due to diabetic retinopathy</p> <p>13. Subject with neovascular/wet age-related macular degeneration</p> <p>14. Subject with an abnormality of the vitreo-retinal interface (eg, vitreomacular traction, epiretinal membranes) with the potential for macular structural damage independent of the inflammatory process</p> <p>15. Subject with a history of active scleritis <math>\leq</math> 12 months of first dose of study drug</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Other Medical Conditions</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p>16. Active IBD within 3 years prior to enrollment</p> <p>17. Active infection or history of infection as follows:</p> <ul style="list-style-type: none"> <li>a. Any active infection for which oral anti-infectives (antibiotics, antivirals, antifungals) were used <math>\leq</math> 14 days prior to first dose of study drug</li> <li>b. A serious infection requiring hospitalization or IV anti-infectives (antibiotics, antivirals, antifungals) <math>\leq</math> 30 days prior to first dose of study drug</li> <li>c. Recurrent or chronic infections or other active infections that in the opinion of the investigator might cause this study to be detrimental to the subject</li> </ul> <p>18. Candida infection requiring systemic treatment <math>\leq</math> 3 months prior to first dose of study drug</p> <p>19. Removed from the protocol version 2.0</p> <p>20. Uncontrolled, clinically significant system disease such as diabetes mellitus, hypertension, cardiovascular disease including moderate to severe heart failure (New York Heart Association class III/IV), moderate to severe renal disease, or moderate to severe liver disease, as determined by investigator</p> <p>21. History of demyelinating disease (including myelitis) or neurological symptoms suggestive of demyelinating disease</p> <p>22. Malignancy within 5 years except treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma</p> <p>23. History or evidence of any clinically significant disorder, condition or disease that, in the opinion of the investigator, may pose a risk to subject safety or interfere with the study evaluation, procedures or completion</p> <p>24. Tuberculosis or fungal infection seen on available chest x-ray taken <math>\leq</math> 3 months of screening or at screening (Exception: documented evidence of completed treatment and clinically resolved)</p> <p>25. Known history of human immunodeficiency virus (HIV)</p> |
| <b>Prior/Concomitant Therapy</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p>26. Prior exposure to izokibep or any other IL-17 inhibitor and IL-17 receptor inhibitors (eg, secukinumab, ixekizumab, bimekizumab and brodalumab)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

27. Prior exposure to biologics that have a potential for or known association with progressive multifocal leukoencephalopathy (ie, natalizumab [Tysabri<sup>®</sup>], rituximab [Rituxan<sup>®</sup>] or efalizumab [Raptiva<sup>®</sup>])
28. Exposure to TNF- $\alpha$  inhibitors, IL-1, IL-12, IL-23, IL-12/23 receptor inhibitors or Janus kinase inhibitors within 5 half-lives prior to first dose of study drug
29. Subject on > 1 concomitant non-biologic non-corticosteroid systemic immunosuppressive therapy at baseline and during the study
30. If entering the study on 1 concomitant immunosuppressive therapy, and the dose has not been stable within the last 4 weeks prior to day 1 or is not within the following allowable doses at day 1:
  - Methotrexate  $\leq$  25 mg per week (oral or SC)
  - Cyclosporine  $\leq$  4 mg/kg/day
  - Mycophenolate mofetil  $\leq$  3 g/day or an equivalent drug to mycophenolate mofetil (eg, mycophenolic acid) at an equivalent dose approved by the medical monitor
  - Azathioprine  $\leq$  175 mg/day
  - Tacrolimus (oral formulation)  $\leq$  8 mg/day
31. Subject has received Retisert<sup>®</sup>, Iluvien<sup>®</sup>, or Yutiq<sup>®</sup> (glucocorticosteroids implant)  $\leq$  3 years prior to the first dose of study drug or has had complications related to the device. The subject has had any of these glucocorticosteroids implant removed  $\leq$  3 months prior to the first dose of study drug or has had complications related to the removal of the device
32. Subject has received intraocular or periocular corticosteroids  $\leq$  3 months prior to the first dose of study drug
33. Subject has received Ozurdex<sup>®</sup> (dexamethasone implant)  $\leq$  6 months prior to the first dose of study drug
34. Subject has received intravitreal methotrexate  $\leq$  3 months prior to the first dose of study drug
35. Subject has received any of the following intravitreal anti-vascular endothelial growth factor (VEGF) therapy or their biosimilars:
  - Lucentis<sup>®</sup> (ranibizumab) or Avastin<sup>®</sup> (bevacizumab)  $\leq$  73 days prior to the first dose of study drug
  - anti-VEGF Trap (aflibercept)  $\leq$  88 days prior to the first dose of study drug
  - or within 84 days of baseline for Beovu<sup>®</sup> (brolucizumab)  $\leq$  112 days prior to the first dose of study drug
36. Subject on systemic carbonic anhydrase inhibitor  $\leq$  1 week prior to screening
37. Subject on cyclophosphamide  $\leq$  30 days prior to the first dose of study drug
38. Any prior or current use of chlorambucil
39. Received live vaccination  $\leq$  12 weeks prior to dosing or scheduled to receive a live vaccine  $\leq$  12 weeks following the last dose of study drug

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| 40. Participating in another clinical study or participated in a clinical study involving administration of a study drug within the following time period prior to dosing: 12 weeks, 5 half-lives or twice the duration of the biological effect of the study drug (whichever is longer)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Diagnostic Assessments</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <p><i>Laboratory abnormalities and measurements</i></p> <p>41. Positive hepatitis B surface antigen (HBsAg) or detected sensitivity on the hepatitis B virus (HBV) DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBcAb)/hepatitis B surface antibody (HBsAb) positive subjects OR positive hepatitis C virus antibody test at screening</p> <p>42. A positive test for syphilis at screening</p> <p>43. Laboratory abnormalities at screening:</p> <ul style="list-style-type: none"> <li>a. Hemoglobin &lt; 9 g/dL</li> <li>b. Platelet count &lt; 100,000/mm<sup>3</sup></li> <li>c. White blood cell count &lt; 3,000 cells/mm<sup>3</sup></li> <li>d. Aspartate aminotransferase and/or alanine aminotransferase <math>\geq</math> 2.5 times the upper limit of normal</li> <li>e. Moderate or severe renal impairment (ie, creatine clearance &lt; 60 mL/min) (Modification of Diet in Renal Disease [MDRD] formula)</li> </ul> <p>Note: Laboratory value(s) out of range due to sampling error or that might be within range after medically appropriate supplementation may be repeated up to 2 times within the screening window before the subject is considered a screen fail.</p> <p>44. Any other laboratory abnormality that in the opinion of the investigator will pose a risk to subject safety or interfere with the study evaluation, procedures or completion</p> |
| <b>Other Exclusions</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <p>45. History of hypersensitivity or allergy to izokibep or its excipients</p> <p>46. History of hypersensitivity or allergy to fluorescein dye</p> <p>47. Previously enrolled, randomized to or withdrawn from this study</p> <p>48. Active substance abuse (drug or alcohol) within 24 weeks prior to first dose of study drug, as determined by the investigator</p> <p>49. Any condition that compromises the ability of the subject to give written informed consent, or the subject's unwillingness or inability to comply with study procedures (ie, subjects who have been placed in an institution on the basis of an official or court order or subject is dependent on the sponsor/investigator or the trial site)</p> <p>50. History of hypersensitivity to prednisone/prednisolone, or any of its excipients</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

### **5.3. Lifestyle Considerations**

The investigator should encourage the subject to limit alcohol consumption to < 2 per day, < 7 alcoholic drinks per week. An alcoholic drink is defined as a 6 oz (177 mL) glass of wine, a 1 oz (30 mL) glass of hard liquor (eg, whiskey) or an 8 oz (237 mL) glass of beer.

### **5.4. Screen Failures**

A screen failure occurs when a subject who consents to participate in the clinical study is not subsequently enrolled/randomized to the study. A minimal set of screen failure information will be collected to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography (ie, age, sex), screen failure reason and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times (ie, total of 3 screens including initial screen). Refer to [Section 6.3.1](#) for details on rescreening.

### **5.5. Criteria for Temporarily Delaying**

Subjects should be dosed within the window as detailed in the SoA ([Section 1.3](#)).

All missed or delayed doses should be documented. If the investigator determines a subject should not be dosed within the defined window for a safety reason (eg, an AE, SAE), then a missed dose should be recorded.

### **5.6. COVID-19-related Precautions**

Risk mitigation measures, including COVID-19-related precautions and procedures (including SARS-CoV-2 testing/screening) will be implemented based on the prevailing situation during the study conduct, at the investigator's discretion and in accordance with local and institutional guidelines as applicable.

Subjects should be routinely monitored for any AEs at every visit, including signs or symptoms of infection. Should subjects demonstrate any symptoms or AEs (including known COVID-19 symptoms or tested positive for COVID-19), the symptoms or AEs will be reported to the site as per study procedures and assessed by the investigator. As with any AEs, AE data will be collected on the appropriate case report form (CRF).

If a subject has received or is planning to receive COVID-19 vaccination, the investigator should refer to vaccine considerations in eligibility criteria ([Section 5.2](#)) and concomitant medications ([Section 6.8](#)) requirements in the protocol.

## 6. Study Drug(s) and Concomitant Therapy

Study drug is defined as any investigational drug(s), marketed product(s), placebo or medical device(s) intended to be administered to a study subject according to the study protocol.

### 6.1. Study Drug(s) Administered

The study drugs include izokibep and matching placebo. In addition, prednisone/prednisolone (or corticosteroid equivalent) will be used as a non-investigational medicinal product.

**Table 3. Study Drug(s) Administered: Izokibep and Placebo**

|                                     | Investigational drug                                                                                                                                                                                                                                                                                                                                    | Placebo                                                                                                                                                                            |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Drug name                           | Izokibep                                                                                                                                                                                                                                                                                                                                                | Placebo to izokibep                                                                                                                                                                |
| Pharmacological group               | Biologic: IL-17A inhibitor                                                                                                                                                                                                                                                                                                                              | None                                                                                                                                                                               |
| Form                                | Solution for injection                                                                                                                                                                                                                                                                                                                                  | Solution for injection                                                                                                                                                             |
| Active ingredient per form          | Each CCI [REDACTED] vial contains CCI [REDACTED] of izokibep (nominal concentration CCI [REDACTED] $\pm$ 10%)                                                                                                                                                                                                                                           | Not applicable                                                                                                                                                                     |
| Route of administration             | SC                                                                                                                                                                                                                                                                                                                                                      | SC                                                                                                                                                                                 |
| Non-active ingredients (excipients) | CCI [REDACTED]<br>CCI [REDACTED]<br>CCI [REDACTED]                                                                                                                                                                                                                                                                                                      | CCI [REDACTED]<br>CCI [REDACTED]<br>CCI [REDACTED]                                                                                                                                 |
| Special storage recommendations     | Vials are to be stored at 2°C to 8°C. The filled syringe must be stored in the refrigerator at 2°C to 8°C (protected from light) if not used for immediate dose administration. Once removed from the refrigerator, the solution should be allowed to warm to room temperature (about 15 to 20 minutes). For further details, refer to Pharmacy Manual. | Can be stored at room temperature (do not store above 25°C). However, given placebo and izokibep will be provided in blinded, matching vials, both should be stored at 2°C to 8°C. |

EDTA = ethylenediaminetetraacetic acid; IL-17A = interleukin 17A; NaCl = sodium chloride; SC = subcutaneous

#### Non-investigational Medicinal Product

Commercially available prednisone/prednisolone (or corticosteroid equivalent) will be sourced locally. Prednisone/prednisolone will be administered orally daily for the first 15 weeks of the study.

#### 6.1.1. Dosage, Administration and Schedule: Izokibep and Placebo

Study drug (izokibep CCI [REDACTED] QW or placebo) will be dosed by SC injection. Study drug vials for placebo and izokibep will be visually indistinguishable.

Study drug doses are fixed and will not be adjusted for individual subjects during the study. Throughout the treatment period, 2 SC injections are to be given for each study drug administration. The anatomical sites for administration of study drug are the upper arm, upper thigh or abdomen.

At the study-site, only authorized investigational site study staff members are to administer study drug (see [Section 6.2](#)). Subjects should be monitored for 1 hour after the first 2 doses of study drug.

Subjects will be randomized to 1 of 2 dosing groups as follows:

- Group 1: placebo QW from day 1/week 0 to week 51
- Group 2: izokibep CCI QW from day 1/week 0 to week 51

The dosing schedule is described by a schema in [Section 1.2](#).

### 6.1.2. Dosage, Administration and Schedule: Prednisone/Prednisolone

Subjects entering the study will have been on a stable dose of oral prednisone/prednisolone  $\geq 7.5$  mg/day to  $\leq 40$  mg/day or equivalent (see [Section 10.7](#) for corticosteroid equivalent doses), for at least 2 weeks prior to day 1/randomization. After randomization, oral prednisone/prednisolone will be taken daily as commercially available oral tablets.

From day 1 (week 0), all subjects will receive a burst of 60 mg/day oral prednisone/prednisolone. By week 2 (day 15), subjects must begin a mandatory stepwise tapering such that the subject will be off prednisone/prednisolone by the start of week 15.

The prednisone/prednisolone taper will be completed as follows:

- By week 5, dose must be  $\leq 20$  mg/day
- By week 10, dose must be  $\leq 5$  mg/day and
- By week 15, subjects will have completely come off prednisone/prednisolone.

An example of the tapering scheduled for oral prednisone/prednisolone is provided in [Table 4](#).

**Table 4. Example Tapering Schedule of Oral Prednisone/Prednisolone**

| Week (Days)     | Prednisone/Prednisolone Dose per Day |
|-----------------|--------------------------------------|
| 0 (1 to 7)      | 60 mg                                |
| 1 (8 to 14)     | 50 to 60 mg                          |
| 2 (15 to 21)    | 40 to 50 mg                          |
| 3 (22 to 28)    | 30 to 40 mg                          |
| 4 (29 to 35)    | 20 to 30 mg                          |
| 5 (36 to 42)    | 15 to 20 mg                          |
| 6 (43 to 49)    | 10 to 15 mg                          |
| 7 (50 to 56)    | 7 to 13 mg                           |
| 8 (57 to 63)    | 5 to 10 mg                           |
| 9 (64 to 70)    | 3 to 8 mg                            |
| 10 (71 to 77)   | 2 to 5 mg                            |
| 11 (78 to 84)   | 1 to 4 mg                            |
| 12 (85 to 91)   | 0 to 3 mg                            |
| 13 (92 to 98)   | 0 to 2 mg                            |
| 14 (99 to 105)  | 0 to 1 mg                            |
| 15 (106 to 112) | Off prednisone/prednisolone          |

## **6.2. Preparation, Handling, Storage and Accountability**

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.
- Only subjects randomized in the study may receive study drug. All study drug must be stored prior to dispensing in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation and record maintenance (ie, receipt, reconciliation and final disposition records).
- Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

## **6.3. Measures to Minimize Bias: Randomization and Blinding**

### **6.3.1. Subject Enrollment**

Before subjects begin participation in any study-specific activities/procedures, the sponsor or designee requires a copy of the site's written Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see [Section 10.1.3](#)). All subjects must personally sign and date the ICF before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and registered the subject as enrolled/randomized within the Interactive Response Technology (IXRS) system. The investigator is to document this decision and date in the subject's medical record. The screening period starts when the subject signs and dates the ICF and ends when the subject is enrolled/randomized, or screen failed. The screening period is up to 28 days. Certain initial screening period procedures may be repeated during the original initial screening period. (Note: Repeating procedures during the original initial screening period is a part of screening and is not considered "rescreening"). These procedures include laboratory assessments due to value(s) out of range due to sampling error or that could be within range with repeat sampling.

All subjects who enter the screening period for the study receive a unique subject identification number assigned by the IXRS system. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

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A subject who is determined to be ineligible must be registered as a screen fail in the IXRS system.

### 6.3.2. Rescreening

Investigators may rescreen a subject if the investigator is reasonably certain that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Reasons to rescreen may include but are not limited to the following:

- Laboratory value(s) out of range due to sampling error or that might be within range after medically appropriate supplementation. (Note: Before screen failing and then rescreening the subject, efforts should be made to repeat the laboratory assessment(s) during the original initial screening period).
- The subject has a medical condition that can be stabilized or resolved prior to the repeat screening/rescreening attempt, or
- Additional time is required following the subject's last dose of an excluded medication.

Investigators are encouraged to consult with the medical monitor prior to rescreening subjects for other reasons.

A subject must provide informed consent prior to the initiation of any rescreening procedures only if 30 or more days have elapsed since the date of the subject's initial informed consent. The subject is entered into rescreening in the IXRS system, and all screening procedures must be repeated except as noted in the inclusion/exclusion criteria. A subject may be screened up to 3 times (ie, no more than 2 rescreens). Near to the end of study enrollment, sites may be notified when no additional subjects will be screened or rescreened.

If a subject rescreens, a chest x-ray does not need to be repeated if a previous chest x-ray was performed < 3 months prior to day 1.

If a subject rescreens, hepatitis, TB, HIV, urinalysis, and electrocardiogram (ECG) tests do not need to be repeated if a previous test was performed < 60 days prior to day 1.

### **6.3.3. Randomization**

Subjects will be randomized to the study drug (izokibep or placebo; QW) on day 1 by the IXRS system. Randomization will be based on a schedule generated by the sponsor or sponsor designee before the start of the study and will be centrally executed using the IXRS system. The subject, site personnel and sponsor/Contract Research Organization (CRO) study personnel and designees will be blinded to the randomization treatment group assignment (ie, izokibep or placebo). The randomization dates are to be documented in the subject's medical record.

Randomization will be stratified by any prior treatment with a systemic TNF- $\alpha$  inhibitor (yes/no) and concomitant systemic inflammatory disease (yes/no).

Izokibep and matching placebo will be visually indistinguishable to prevent unblinding during preparation or administration of study material.

Subjects assigned to receive placebo will be randomized in a **1:1** ratio to receive placebo administered QW. This will allow for blinding of test material.

### **6.3.4. Site Personnel Access to Individual Treatment Assignments**

Subject's treatment assignment should be unblinded only when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study-site for any other reason will be considered a protocol deviation. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's drug assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator is strongly encouraged to contact the sponsor to discuss the situation prior to unblinding a subject's drug assignment unless this could delay emergency treatment for the subject. If a subject's drug assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

If an SAE requires an expedited regulatory report be sent to 1 or more regulatory agencies, sponsor/designee's safety staff may unblind the drug assignment for the subject. A copy of the report, identifying the subject's drug assignment, may be sent to that regulatory agency in accordance with local regulations.

Please refer to the Study Pharmacy Manual for details.

## **6.4. Study Drug Compliance**

When subjects are dosed at the site, they will receive study drug directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

When study drug(s) is administered at home by the subject/caregiver, compliance with study drug will be assessed at each visit. Compliance will be assessed by review of the subject dosing diary, during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of study drug dispensed and administered to each subject must be maintained and reconciled with study drug and compliance records. Intervention dose dates, including study drug delays will also be recorded. Partial dose administration will be explained.

## **6.5. Dose Modification**

No dose modifications are allowed in the study.

## **6.6. Continued Access to Study Drug after the End of the Study**

There is no plan to continue access to study drug after the end of study. The choice of further therapy for non-infectious, intermediate-, posterior- or pan-uveitis at the end of the clinical study depends on the subject's individual needs and is left at the physician's discretion.

## **6.7. Overdose**

Excessive dosing of study drug or prednisone/prednisolone (beyond that prescribed in the protocol and including overdose) should be recorded in the CRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

## **6.8. Prior and Concomitant Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including route, dose and frequency

Concomitant medications should be used in alignment with the approved label in the respective country, and per doses as outlined below. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### **6.8.1. Prior Therapies**

Treatments for uveitis since initial diagnosis (as determined through medical history records or through subject interview) prior to study entry will be recorded in the source documents and on the CRF, along with the reason for discontinuation.

The following information on prior uveitis treatments should be captured:

- Any prior biological therapy or Janus kinase inhibitor.
- Any immunosuppressants other than systemic corticosteroids within 4 weeks prior to day 1. In addition, the highest previously administered dose and the date range should also be recorded if it is beyond 4 weeks of first dose.

- For prior systemic corticosteroids, record the dose administered within the 2 weeks prior to day 1. In addition, the highest previously administered dose and the date range should also be recorded if it is beyond 2 weeks of day 1. In addition, the date of the last uveitis flare and the dosage of corticosteroid treatment at the time of the flare must be recorded. If the subject was completely off corticosteroids when the flare occurred, the date of the last dose of corticosteroid prior to flare must be recorded.
- For topical uveitis therapies, record the dose administered within 2 weeks prior to day 1. In addition, the highest previously administered dose and the date range should also be recorded if it is beyond 2 weeks of first dose. The medication name should include the strength, if part of the generic name (eg, betamethasone phosphate 0.1%). The dose should be recorded as number of drops.
- For VEGF therapies, record all doses administered within 1 year prior to study entry.

### 6.8.2. Concomitant Therapies

Subjects will be allowed to continue on 1 ongoing non-biologic immunosuppressive therapy at study entry provided the dose has been stable within the 4 weeks prior to day 1 and must remain unchanged throughout the study. In addition, doses must be within the acceptable limits listed below:

- Methotrexate  $\leq 25$  mg/week
- Cyclosporine  $\leq 4$  mg/kg/day
- Mycophenolate mofetil  $\leq 3$  g/day
- Azathioprine  $\leq 175$  mg/day
- Tacrolimus (oral formulation)  $\leq 8$  mg/day

There is no required washout period for the discontinued concomitant immunosuppressive.

Subjects who enter the study receiving topical corticosteroids (eye drops) will undergo a standardized taper schedule beginning at week 1 until all subjects are off topical corticosteroids by week 10. Depending on the dose that the subject is on at day 1 visit, the number of drops per day will be decreased every week until eye drops are discontinued by week 10. An example tapering schedule is provided in [Table 5](#).

Investigators can consider supplementation in line with standard medical practice, with agents such as calcium, Vitamin D3 and proton pump inhibitors, as appropriate, if there is a concern for or clinical suspicion or evidence of osteopenia or gastritis.

Subjects who meet the treatment failure criteria may receive rescue medications at the investigator's discretion. If the rescue medication is a biologic, the subject must discontinue from study drug and all activities listed in the early termination visit (week 52) must be completed within 2 weeks. If the rescue medication is a non-biologic, the subject can continue on study and continue receiving study drug. Subjects should continue to complete study assessments as outlined in the SoA ([Section 1.3](#)). Only the efficacy assessments of BCVA and VFQ-25 will be completed at week 24 and week 52; all other efficacy assessments will not be completed.

**Table 5. Example Tapering Schedule of Topical Corticosteroids**

| Dose (No. of drops/day) per Week |
|----------------------------------|
| 12                               |
| 10                               |
| 8                                |
| 6                                |
| 5                                |
| 4                                |
| 3                                |
| 2                                |
| 1                                |
| Eye drops discontinued           |

**6.8.3. Prohibited Medications**

The following medications are prohibited from enrollment through week 52:

- All other biologic therapies with a potential therapeutic impact on uveitis including but not limited to:
  - TNF- $\alpha$  inhibitors (eg, adalimumab, etanercept, infliximab, golimumab)
  - Abatacept
  - Secukinumab
  - Ixekizumab
  - Bimekizumab
  - Anakinra
  - Rituximab
  - Natalizumab
  - Tocilizumab
  - Certolizumab pegol
  - Ustekinumab
  - Belimumab
- Anti-VEGF therapy
- All other immunosuppressive therapy other than methotrexate, cyclosporine, mycophenolate mofetil or an equivalent drug to mycophenolate mofetil (eg, mycophenolic acid) at an equivalent dose, azathioprine and tacrolimus (oral formulation)
- Live vaccines (during the study and for 2 months after the last dose of study drug)
- Implantable corticosteroids
- Any investigational agents
- Procedures including:
  - refractive laser surgery
  - retinal laser photocoagulation
  - neodymium-doped yttrium aluminum garnet posterior capsulotomy
  - laser surgery of the macula including photodynamic therapy or focal laser photocoagulation

## 7. Discontinuation of Study Drug and Subject Discontinuation/ Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in [Section 10.1.8](#).

### 7.1. Discontinuation of Study Drug

It may be necessary for a subject to permanently discontinue study drug. The reason for permanent discontinuation of study drug will be documented.

Reasons for removal from study drug include any of the following:

- Subject request (withdrawal of consent)
- Safety concern (eg, due to an AE [including laboratory abnormality], ineligibility determined, protocol deviation, noncompliance, pregnancy, hepatotoxicity)
- Death
- Lost to follow-up
- Study terminated by sponsor
- Subject who meets the criteria of non-response
- Subject who meets the criteria of treatment failure and receives a biologic as a rescue medication

Subjects with newly diagnosed IBD or with IBD flares during the study must:

- Discontinue study drug and be followed-up until resolution of active IBD symptoms
- Be referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist

Subjects who meet non-response criteria or treatment failure and received a biologic as a rescue medication must complete the early termination visit (week 52) within 2 weeks. Subjects are encouraged to complete the follow-up period consisting of 2 visits: an 8-week follow-up visit ( $\pm 5$  days) after the last dose of study drug for safety and collection of pregnancy information. In addition, a 14-week follow-up visit ( $\pm 5$  days) for collection of PK and ADA samples.

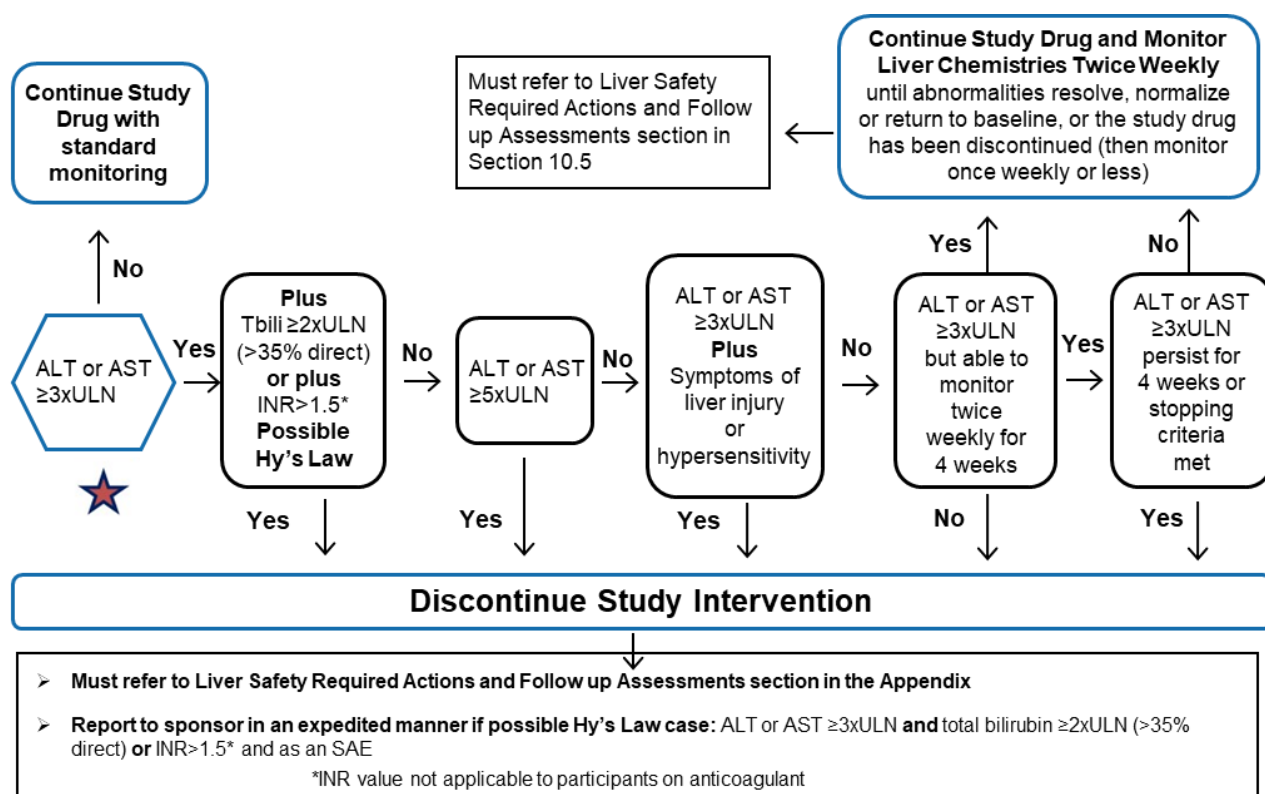
For subjects who meet treatment failure and receive rescue medication, which is a non-biologic, the subject can continue on study and continue receiving study drug. For these subjects, assessments as outlined in the SoA ([Section 1.3](#)) should be followed, with the exception of efficacy assessments. Only efficacy assessments of BCVA and VFQ-25 will be completed at weeks 24 and 52, and no other efficacy assessments will be completed.

If study drug is permanently discontinued for all other reasons, the subject will be encouraged to remain in the study to be evaluated for safety and efficacy. Subjects should continue to complete study assessments as outlined in the SoA ([Section 1.3](#)) where possible, with the exception of study drug administration. Study visits at weeks 10, 24, 48 and 52 should be prioritized.

### 7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study drug for abnormal liver tests is required by the investigator when a subject meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in the best interest of the subject (Figure 2). The investigator may consider rechallenge if a reasonable alternative explanation is identified and after consultation with the medical monitor.

**Figure 2. Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm<sup>1</sup>**



ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; SAE = serious adverse event; Tbili = total bilirubin; ULN = upper limit of normal

<sup>1</sup> Liver Safety: Required actions and follow-up assessments can be found in [Section 10.5](#).

### 7.1.2. Study Drug Restart or Rechallenge After Liver Stopping Criteria Are Met

Study drug restart/rechallenge after liver chemistry stopping criteria are met is allowed in this study. If the subject meets liver chemistry stopping criteria, do not restart/rechallenge the subject with study drug unless:

- Sponsor medical monitor approval **is granted**
- IEC and/or IRB approval is obtained, if required

NOTE: If study drug was interrupted for suspected study drug-induced liver injury, the subject should be informed of the risk of death, liver transplantation, hospitalization and jaundice before resumption of dosing.

Refer to [Section 10.5](#) Liver Safety: Required Actions and Follow-up Assessments and Study drug Restart/Rechallenge Guidelines for details on the restart/rechallenge process.

If sponsor medical monitor approval to restart/rechallenge the subject with study drug is **not granted**, then the subject must permanently discontinue study drug and may continue in the study for protocol-specified study assessments.

## 7.2. Subject Discontinuation/Withdrawal from the Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Decision by investigator (following discussion with sponsor for reasons other than non-response and treatment failure)
- Death
- Withdrawal of consent from study
- Lost to follow-up

Withdrawal of consent from study:

- A subject may withdraw from the study at any time without jeopardizing subsequent medical care.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA ([Section 1.3](#)). See the SoA ([Section 1.3](#)) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The subject will be permanently discontinued from the study drug and the study at that time.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and notify the sponsor or its designee.

### **7.3. Lost to Follow-up**

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study-site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 attempts at known effective points of contact [eg, phone, email, text], and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered lost to follow-up.

## 8. Study Assessments and Procedures

- Informed consent must be obtained before any study-related procedures are performed. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by the subject.
- Study procedures and their timing are summarized in the SoA ([Section 1.3](#)). Protocol waivers or exemptions are not allowed.
- All assessments are to be completed before study drug administration, unless otherwise specified. It is recommended that patient-reported outcome assessments be completed first.
- The order of the eye examinations may occur according to established site procedures as long as the slit lamp examination for anterior chamber cell (ACC) count is performed prior to the application of mydriatic eye drops to dilate the subject's pupils for further assessment.
- At screening, the central reading center assessment based on fundus photography, FA ([Section 8.1.7](#)) and/or SD-OCT ([Section 8.1.5](#)) is required to confirm eligibility prior to day 1.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA ([Section 1.3](#)), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, x-rays) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the SoA ([Section 1.3](#)).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

### 8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA ([Section 1.3](#)). The order of the eye examinations may occur according to established site procedures. However, paracenteses of anterior chamber fluid should not be performed until after all examinations and testing have been completed, including FA. This test series is to be completed prior to study drug administration and oral prednisone/prednisolone.

These tests must be performed by named, qualified, health care professional member(s) of the site's study team. If possible, all evaluations for a specific test procedure within a subject are to

be performed by the same authorized member of the site's team, using the same equipment. If a staff member who was involved in these tests leaves the site, appropriate measures should be taken to assign and train a successor who continues the testing already started with the least possible disruption while well-adherent to the originally agreed standardization rulings.

Independent sequential masked efficacy evaluations by the central reading center will be established for SD-OCT, fundus photography and FA measurement in order to standardize and strengthen the validity of efficacy evaluations.

For the purpose of the efficacy endpoints and assessment of non-response, the principal investigator's assessment of vitreous haze and inflammatory lesions, based on fundus photographs, and if required FA and/or SD-OCT, will take precedence over the central reading center assessment of vitreous haze and inflammatory lesions.

If a subject meets non-response criteria during the eye examination, all activities listed in the early termination visit (week 52) must be completed within 2 weeks.

#### **8.1.1. Best Corrected Visual Acuity**

Refraction and assessment of BCVA will be assessed at the timepoints indicated in the SoA ([Section 1.3](#)). At each visit, subjects should undergo refraction and result of refraction for each eye recorded on the CRF. Using the appropriate corrective lenses based on the visit's refraction, the subject's BCVA is measured using an ETDRS chart. Please refer to the Visual Acuity Manual provided by the sponsor/designee for instructions.

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## 8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA ([Section 1.3](#)).

### 8.2.1. Medical and Surgical History

A complete medical and surgical history, as well as history of alcohol and nicotine use, will be obtained from each subject during the screening visit. An updated medical history will be obtained at the day 1 visit prior to study drug administration and updated as necessary throughout the study.

A uveitis history obtained at screening will capture date of onset of uveitis, which eye(s) is/are affected, type of uveitis, the nature of diagnosis, subject history of infectious uveitis, cause of previous infection (if applicable), number of flares within the past 12 months (including the current flare), date of last flare prior to current flare, prednisone/prednisolone dose at time of last flare (or equivalent prednisone/prednisolone dose), if subject was on another corticosteroid (refer to [Section 10.7](#)), and date of onset of current flare.

### 8.2.2. Physical Examination

A complete physical examination will include, at a minimum, assessments of the dermatological, cardiovascular, respiratory, gastrointestinal and neurological systems. At specified timepoints in the SoA ([Section 1.3](#)), physical examinations will also include assessment of skin and mucus membranes.

Clinically significant findings observed prior to first dose of study drug should be listed as medical history in the CRF and reported as AEs if observed after first dose of study drug.

### 8.2.3. Physical Measurements

Height and weight measurements are to be performed at the timepoints indicated in the SoA ([Section 1.3](#)) and data will be recorded in cm and kg, respectively. Height and weight are to be measured without shoes.

### 8.2.4. Vital Signs

Vital signs will be measured in a sitting position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, pulse and respiratory rate.

### 8.2.5. Electrocardiograms

Triple 12-lead ECGs will be obtained as outlined in the SoA ([Section 1.3](#)) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT intervals.

### 8.2.6. Clinical Safety Laboratory Tests

- See [Section 10.2](#) for the list of clinical laboratory tests to be performed and the SoA ([Section 1.3](#)) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - a. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - b. All protocol-required laboratory tests, as defined in [Section 10.2](#), must be conducted in accordance with the laboratory manual and the SoA ([Section 1.3](#)).
  - c. If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded within source documents.

#### **8.2.6.1. Pregnancy Testing**

- Refer to [Section 5.1](#) Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing in WOCBP will be conducted throughout the study. A serum pregnancy test will be performed at screening and urine pregnancy testing will be performed at subsequent visits as detailed in the SoA ([Section 1.3](#)).
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation or regulatory agency, to establish the absence of pregnancy at any time during the subject's participation in the study.
- The investigator is responsible for review of medical history, menstrual history and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

#### **8.2.6.2. Hepatitis Testing**

All subjects will be tested for the presence of HBV and hepatitis C virus at screening. A positive result for HBsAg will be exclusionary. Samples negative for HBsAg will be tested for HBsAb and HBcAb. If test results are positive for HBcAb or HBsAb, then HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

#### **8.2.6.3. Antinuclear Antibodies/Anti-double-stranded DNA**

Blood for antinuclear antibodies (ANAs)/anti-double-stranded DNA will be collected at screening. These tests are markers, and the results are not exclusionary; therefore, waiting for the results should not delay enrollment or randomization. If a subject develops signs and symptoms of lupus on study, an ANA test may be repeated based on the investigator's clinical judgment.

**8.2.6.4. Herpes Simplex Virus (Immunoglobulin M/Immunoglobulin G)**

Subjects will be tested for herpes simplex virus to rule out a potential infectious etiology of the uveitis.

**8.2.6.5. Varicella Zoster Virus (Immunoglobulin M/Immunoglobulin G)**

Subjects will be tested for varicella zoster virus to rule out a potential infectious etiology of the uveitis.

**8.2.7. Home Study Drug Administration Diary**

Study-site staff will administer study drug at the first 2 visits. Thereafter, if home dosing is a consideration, the subject or subject's caregiver or designee must administer and demonstrate competency for at least 2 visits prior to being allowed to dose at home. Otherwise, the subject will need to return to the site for all injections. The subject (or caregiver/designee) will complete a diary for every study dose taken outside of the study-site (ie, at home). The study drug should be administered on the dates as directed by the site staff. Information regarding the study drug administration (eg, date and time of study drug administration, if the full dose was administered) will be recorded on the study drug administration diary. Instructions on proper study drug administration will be provided to the subject (caregiver/designee). Subjects will be instructed to call the study-site if they are having problems administering the study drug or have missed or delayed administering a dose. Subjects will be instructed to bring the study drug administration diary to each study visit.

**8.3. Adverse Events, Serious Adverse Events and Other Safety Reporting**

The definitions of AEs and SAEs can be found in [Section 10.3](#).

Adverse events will be reported by the subject (or, when appropriate, by a caregiver or surrogate).

The investigator and any qualified designees are responsible for detecting, documenting and recording events that meet the definition of an AE or SAE. The investigator is responsible for following up all AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue the study drug (see [Section 7](#)).

The method of recording, evaluating and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Section 10.3](#).

**8.3.1. Time Period and Frequency for Collecting AE and SAE Information**

All SAEs will be collected from the signing of the ICF until the 8-week follow-up visit at the timepoints specified in the SoA ([Section 1.3](#)).

All AEs will be collected from the first dose of study drug until the 4 weeks after the last dose of study drug as specified in the SoA ([Section 1.3](#)).

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from investigator's knowledge of the event, as indicated in [Section 10.3.4](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor/designee (see [Section 10.3.4](#)).

### **8.3.2. Method of Detecting AEs and SAEs**

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

### **8.3.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in [Section 8.3.6](#)) will be followed until resolution, stabilization, the event is otherwise explained or the subject is lost to follow-up (as defined in [Section 7.3](#)). Further information on follow-up procedures is provided in [Section 10.3.3](#).

### **8.3.4. Regulatory Reporting Requirements for SAEs**

- Prompt notification by the investigator to the sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs and investigators. This includes reporting of events that meet suspected unexpected serious adverse reaction (SUSAR) criteria via Eudravigilance, as applicable.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor or designee will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor or designee policy and forwarded to investigators as necessary.

**8.3.5. Pregnancy**

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study drug and until 8 weeks after the last dose of study drug.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The subject/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject/pregnant female partner and the neonate, and the information will be forwarded to the sponsor or designee.
- Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor or designee as described in [Section 8.3.4](#). While the investigator is not obligated to actively seek this information in former study subjects/pregnant female partners, he/she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study drug.

**8.3.6. Adverse Events of Special Interest**

Based on the class effects or potential risks with IL-17 inhibitors, the following events of special interest will be monitored:

- Candida infection
- IBD
- Suicidal ideation
- Malignancies
- Major cardiovascular and cerebrovascular events (cerebrovascular accident and transient ischemic attack, non-fatal myocardial infarction or unstable angina, and cardiovascular death)
- TB
- Infections (opportunistic, serious, or fungal only)

- Cytopenias (anemia, neutropenia, lymphopenia, monocytopenia, thrombocytopenia)
- Systemic hypersensitivity reactions

## 8.4. Pharmacokinetic Assessments

- Blood samples will be collected for measurement of plasma concentrations of izokibep as specified in the SoA ([Section 1.3](#)).
- Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual by the sponsor or designee. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of izokibep. Each plasma sample will be divided into 2 aliquots (1 each for PK, and a backup). Samples collected for analyses of izokibep (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples.
- Study drug concentration information will not be reported to investigative sites.
- Pharmacokinetic samples collected may be used for assay validation and related assay development purposes.
- Pharmacokinetic samples will be shipped frozen from clinical sites to the central laboratory and later shipped from the central laboratory to the PK laboratory for analysis. The PK plasma samples will be stored in a secure storage space with adequate measures to protect confidentiality.
- The PK samples will be retained while research on izokibep or study drugs of this class or uveitis continues but no longer than 20 years or other period as per local requirements.

## 8.5. Genetics

Not applicable.

## 8.6. Biomarker Assessments

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## 9. Statistical Considerations

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

### 9.1. Statistical Hypotheses

The hypotheses to be tested for the primary endpoint are:

$H_0: \lambda_{Izo} / \lambda_{Pbo} = 1$  versus  $H_0: \lambda_{Izo} / \lambda_{Pbo} \neq 1$

where  $\lambda_{Izo}$  and  $\lambda_{Pbo}$  are the hazard rates for 1 regimen of izokibep and combined regimens of placebo, respectively.

The hypotheses to be tested for the first secondary endpoint of change in BCVA are:

$H_0: \mu_{Izo} - \mu_{Pbo} = 0$  versus  $H_0: \mu_{Izo} - \mu_{Pbo} \neq 0$

where  $\mu_{Izo}$  and  $\mu_{Pbo}$  are the mean changes in BCVA in an eye for 1 regimen of izokibep and combined regimens of placebo, respectively. Analogous hypotheses will be tested for the second secondary endpoint of change in NEI-VFQ-25 in a subject at week 24, the third secondary endpoint of change in SD-OCT in an eye at week 10, the fourth secondary endpoint of change in SD-OCT in an eye at week 52, and the fifth secondary endpoint of quiescence rate at week 10.

#### 9.1.1. Multiplicity Adjustment and Type I Error Rate

Hypothesis tests will be adjusted to control the familywise error rate in the strong sense at  $\alpha = 0.050$ , 2 sided.

As described in [Section 9.4](#), an adjustment of 0.0001 will be made to account for the unblinded data summaries reviewed by the DMC. The hypotheses will therefore be tested at  $\alpha = 0.0499$ .

The statistical comparisons of the primary efficacy endpoint and the secondary endpoints will be carried out in sequential order. All endpoints starting with the primary endpoint and moving through the secondary endpoints will be tested sequentially for comparison of izokibep dosed QW to placebo. For each comparison, significance concluded if  $p < 0.0499$  and if all prior comparisons in the testing sequence also showed  $p < 0.0499$ . Specifically, the testing order will be:

- The primary endpoint, time to treatment failure, comparing izokibep dosed QW to placebo dosed QW.
- The first secondary endpoint, change in BCVA, comparing izokibep dosed QW to placebo dosed QW.
- The second secondary endpoint, change in NEI-VFQ-25, comparing izokibep dosed QW to placebo dosed QW.
- The third secondary endpoint, change in CRT at week 10, comparing izokibep dosed QW to placebo dosed QW.

- The fourth secondary endpoint, change in CRT at week 52, comparing izokibep dosed QW to placebo dosed QW.
- The fifth secondary endpoint, quiescence at week 10, comparing izokibep dosed QW to placebo dosed QW.

If a hypothesis is not rejected, p-values for subsequent hypotheses in the sequence will be reported but will not be used to assess objectives or make determinations of efficacy. For any subjects enrolled before amendment v2.0 and randomized to receive izokibep Q2W, these efficacy data will be listed but not used in any summaries or comparisons.

## 9.2. Analysis Sets

### Full Analysis Set

For assessing the primary and secondary efficacy objectives, all subjects randomized will be included in the analyses as the Full Analysis Set. Intercurrent events (ICEs) such as missed or discontinued treatment and protocol deviations will be addressed as described in the definition of the estimands in [Section 9.3](#). Subjects will be included according to randomized treatment assignment.

### Safety Analysis Set

For assessing the safety objectives, all subjects randomized who receive at least 1 administration of test material will be included in the summaries and analyses. In the event that a subject receives incorrect study drug, that subject will be grouped according to treatment received, and such subjects will be listed and counted in the final report.

### PK Analysis Set

For assessing PK parameters, all subjects who receive at least 1 administration of test material and have at least 1 sample collected and analyzed for drug concentration will be included in summaries and analyses.

### ADA Analysis Set

For assessing ADA, all subjects who receive at least 1 administration of test material and have both baseline ADA and at least 1 post-dose ADA measurement will be included in summaries and analyses.

## 9.3. Statistical Analyses

### 9.3.1. General Considerations

All data collected will be summarized by planned timepoint without imputation. Continuous data will be summarized with count, mean, median, standard deviation, minimum and maximum. Change from baseline will additionally include standard error. Categorical data will be summarized with count and percent. Time to event data will be summarized with product-limit estimators of median and quartiles. Placebo subjects assigned to receive doses QW will be summarized both separately and combined, with hypotheses tested using both placebo dosing frequencies combined. All hypothesis tests will be reported with 2-sided p-values. Comparison of QW dosing to placebo will use only subjects assigned to receive izokibep QW or placebo. All

confidence intervals will be 2-sided with nominal 95% coverage. Data will be summarized by planned timepoint, using data collected at the visit. Study day will be calculated as post-baseline date minus randomization date, plus 1 (except that study day for pre-randomization dates will not include the plus 1). Day range windows will not be applied for summaries (but may be applied for protocol deviations). Baseline values will be the last value collected before randomization and change from baseline will be calculated as post-baseline value minus baseline value. Stratified tests will use the 2 strata from the randomization process. If a subject is incorrectly classified into a stratum during the randomization process, the analysis will use the correct classification, not the classification used during randomization.

### 9.3.2. Primary Endpoint and Estimand

The primary endpoint is time to treatment failure. A subject is defined as reaching time to treatment failure by meeting  $\geq 1$  of the 4 criteria below in at least 1 eye:

| Criteria                                                                 | Time to Treatment Failure                                                                                                                                                                  |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions | New active, inflammatory lesions, or worsening of previously identified inflammatory lesions, relative to baseline                                                                         |
| ACC count (SUN Grade)                                                    | $\geq 1$ -grade increase (worsening) from baseline prior to Week 10 OR a 2-step increase relative to best state achieved up to but not including Week 10 at all visits at or after Week 10 |
| Vitreous haze (NEI/SUN Grade)                                            | $\geq 1$ -grade increase (worsening) from baseline prior to Week 10 OR a 2-step increase relative to best state achieved up to but not including Week 10 at all visits at or after Week 10 |
| Visual acuity (ETDRS)                                                    | Worsening of BCVA by $\geq 15$ letters relative to the best state achieved up to but not including Week 10                                                                                 |

The primary analysis will occur when all subjects have had the opportunity to complete the week 24 visit or discontinued the study. The treatment policy strategy for ICEs will be used in general to define the estimand, so subjects will be included using observed treatment failure data regardless of treatment compliance, use of rescue medications or any other protocol deviations. Subjects who discontinue the study or who have not completed week 52 at the time of the primary analysis will be censored at the last assessment. The population for the estimand will be all subjects randomized.

The null hypothesis of equal hazard rates will compare each dosing regimen of izokibep to the combined placebo group using the logrank test. Factors used for stratification of the randomization will be included as strata in the model.

Supportive analyses using other assumptions about ICEs (including use of prohibited concomitant medications due to efficacy considerations, inability to taper steroids due to efficacy considerations, withdrawal from treatment due to lack of efficacy and AEs related to treatment) will also be reported. These will be defined before the database is locked and treatment assignments are unblinded for the primary analysis.

### 9.3.3. Secondary Endpoints and Estimands

The secondary endpoints are change in BCVA at week 24, change in NEI-VFQ-25 at week 24, change in CRT at week 10, change in CRT at week 52, and quiescence at week 10. The treatment policy strategy for ICEs will be used to construct estimands for each. Unlike the primary endpoint estimand, subjects who are early treatment failures will not be excluded from the population for any secondary endpoint. For change in BCVA at week 24, change in CRT at week 10, and change in CRT at week 52, the analysis unit will be eye and analyses will include all eyes from subjects that meet entry criteria; for quiescence rate at week 10 and change in NEI-VFQ-25 at week 24, the analysis unit will be subject.

The secondary endpoints of change in BCVA, change in NEI-VFQ-25 and change in CRT will be analyzed as continuous variables. The baseline value for change will be the best reported value, including all timepoints starting with the last value obtained before randomization through the last value obtained before week 10 for BCVA and NEI-VFQ-25. Change in CRT will include all timepoints starting with the last value obtained before randomization through the last value obtained at or before week 10. Change at week 24 (week 52) will be calculated as week 24 (week 52) value minus baseline value. The analysis will be reported using mixed effects model with repeated measures (MMRM), using observed change at all scheduled assessments at and after week 10, up to and including week 24, and using eye within subject as a nested effect to account for correlation between eyes within a subject for BCVA and CRT. A contrast at week 24 will be used to estimate the effect at week 24. Covariates in the MMRM analysis will be the stratification factors used in the randomization and the baseline value. Eyes (BCVA and CRT) or subjects (NEI-VFQ-25) with no values at or after week 10 will be included by imputing a change of 0 at the first planned assessment at or after week 10.

The fifth secondary endpoint of quiescence at week 10 will be analyzed in a stratified analysis. Within each of the 4 strata used for the randomization, the risk difference and associated standard error will be calculated. The analysis will combine the 4 risk differences using Cochran-Mantel-Haenszel weighting, assuming a common risk difference within each of the strata. The 4 standard errors will similarly be combined, and the test statistic will be calculated. Subjects who do not have an assessment for quiescence at week 10 will be included as non-responders (nonresponse imputation [NRI]). The number of subjects included with NRI will be reported by treatment group, along with reasons for missed assessments.

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### 9.3.5. Safety Analyses

Safety data will include summaries of exposure, AEs, SAEs and laboratory data. Subjects who received placebo QW will be used for summaries during the placebo-controlled portion of the study. Subjects who received izokibep Q2W before initiation of protocol amendment v2.0 will be listed only. No inferential statistics (p-values) will be reported for safety data.

Exposure will include the number of doses administered (including complete and incomplete doses) and reasons for missed or incomplete doses. Exposure will be reported through the planned collection of the primary endpoint and for the entire study.

Serious AEs reported before first administration of study drug will be listed. All summaries will include only treatment-emergent events. The number of subjects who report 1 or more AEs, the number who report 1 or more severe AEs, the number who report 1 or more SAEs and the number who report 1 or more AEs that leads to discontinuation of study drug will be summarized by treatment during the primary phase of the study and overall.

Laboratory data including ADAs will be summarized at each planned collection timepoint.

## 9.4. Interim Analysis and Early Stopping Rules

No interim analyses will be conducted for the purpose of stopping the study or altering the study design.

The primary analysis of primary and secondary endpoints will occur after all subjects have had an opportunity to complete the week 24 assessments (have completed the week 24 assessments, or have completed a subsequent timepoint assessment, or permanently discontinued the study before week 24). For the secondary endpoints, this will include all data for all subjects for the final analysis, and so it will be the final analysis. For the primary endpoint, all available data at visits after week 24 will be included, but some subjects will be ongoing and may have data collected after the primary analysis is reported. All data collected for the primary endpoint for all subjects through week 52 will be reported in a subsequent analysis, but the p-values from each comparison of a regimen of izokibep to placebo in this subsequent analysis will not be used for any alpha-preserving hypothesis testing. Investigators, site personnel and all sponsor personnel who have contact with subjects will remain blinded to individual subject treatment assignments until the final analysis.

When the primary efficacy analysis is conducted, safety data will be summarized. Summaries will include all safety data through week 24 and all available data on all subjects through

week 52. All safety data will be summarized through week 52 when all subjects have completed through week 52.

### **9.5. Sample Size Determination**

The analysis as planned will use a CCI . An assessment of power by the CCI , assuming a hazard ratio of CCI and a CCI dropout rate at CCI (treated as censored in the analysis), results in CCI power, using only events through CCI and calculated using CCI and Sample Size software. Events in some subjects after week 24 will be included, further increasing the power.

## **10. Supporting Documentation and Operational Considerations**

### **10.1. Regulatory, Ethical and Study Oversight Considerations**

#### **10.1.1. Regulatory and Ethical Considerations**

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's Brochure and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- Approval for protocols and any substantial amendments to the protocol that require health authority approval prior to initiation will be obtained except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable) and all other applicable local regulations.

#### **10.1.2. Financial Disclosure**

Investigators and subinvestigators will provide the sponsor or designee with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

**10.1.3. Informed Consent Process**

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

**10.1.4. Data Protection**

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that the subject's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that the subject's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members and by inspectors from regulatory authorities.
- The sponsor and investigator will implement appropriate measures to monitor and identify any breach of security leading to accidental or unlawful destruction, loss, alteration, unauthorized disclosure or access to that data. In the event of a personal data breach, the sponsor and investigator will take appropriate measures to address the breach, including measures to mitigate its adverse effects. The investigator will notify the sponsor without undue delay after having become aware of the breach. Such notification will contain the details of a contact point where more information can be obtained, a description of the nature of the breach (including, where possible, categories and approximate number of data subjects and personal data records concerned), its likely consequences and the measures taken or proposed to address the breach including, where appropriate, measures to mitigate its possible adverse effects. Upon becoming aware of any data breach, the sponsor will notify all competent data protection authorities of the breach, where required by local regulations. Where feasible and permissible by applicable law, such notification will occur within 72 hours of becoming aware of the breach. Such notification will contain the details of a contact point where more information can be obtained, a description of the nature of the breach (including, where possible, categories and approximate number of data subjects and personal data records

concerned), its likely consequences and the measures taken or proposed to address the breach including, where appropriate, measures to mitigate its possible adverse effects.

- Taking into account the nature, scope, context and purpose of the processing, and the risks for the rights and freedoms of natural persons, the investigator will implement technical and organizational measures to ensure adequate security and confidentiality of the data. Such measures will include without limitation pseudonymization and data encryption in transit and at rest, identity and access management procedures to restrict physical and logical access to the data, network perimeter and endpoint protection using firewalls and other intrusion detection systems, documented policies taking account of the state of the art, and regular training of all personnel responsible for the processing of personal data.

#### **10.1.5. Dissemination of Clinical Study Data**

The results of the study will be reported in a clinical study report generated by the sponsor and will contain CRF data from all study sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study subject identifiers will not be used in publication of results. Any work created in connection with the performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator see [Section 10.1.9](#)) shall be the property of the sponsor as author and owner of copyright in such work.

#### **Registration of Clinical Studies and Disclosure of Results**

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law including posting company-sponsored study information in the US National Institutes of Health website [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

#### **10.1.6. Monitoring and Data Quality Assurance**

- Qualified, assigned monitors from the sponsor (or designee) will conduct regular on-site and remote monitoring visits to monitor various aspects of the study. These visits and communications, along with regular inspection of the electronic CRFs, will be conducted to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the electronic CRFs, verification of data against source documents, and occurrence of AEs, etc. The investigator must provide the monitor with full access to all source and study documents.
- All subject data relating to the study will be recorded on CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.
- Guidance on completion of CRFs will be provided.
- The investigator or site staff will promptly report to the sponsor (or designee) all deviations that occur at their clinical site, and report protocol deviations to their IRB/IEC according to local requirements.

- The sponsor (or designee) may audit investigator sites regarding, but not limited to, the informed consent process, presence of required documents, adherence to protocol, accountability and storage of drug supplies, comparison between electronic CRF with source documents, etc. All medical records and study-related documents must be available for audit, and the investigator and study staff agree to participate and cooperate in audits conducted in a reasonable manner.
- Government regulatory authorities and ethics committees may also inspect the investigator site during or after the study. The investigator or designee should contact the sponsor (or its designee) immediately if this occurs. The investigator must cooperate fully with regulatory authorities or other audits conducted in a reasonable manner.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.
- No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- Quality Tolerance Limits will be defined before the start of the study and monitored by the CRO and sponsor during the course of the study. They will also be reported in the clinical study report.

#### **10.1.7. Source Documents**

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments. Information from medical records and other source documents will be promptly transcribed to the appropriate section of the electronic CRF. The electronic CRF is not considered and should not be used as source documentation.
- Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

#### **10.1.8. Study and Site Start and Closure**

##### **Study Start**

The study start date is the date on which the first subject is enrolled into the study.

##### **Study/Site Termination**

The sponsor reserves the right to close the study-site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study-site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study-site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
- Total number of subjects included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator should promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

**10.1.9. Publication Policy**

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments. The clinical study agreement/site contract will cover additional details regarding publications.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements.

**10.2. Clinical Laboratory Tests**

- The tests detailed in [Table 9](#) will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in [Section 5](#) of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Table 9. Protocol-required Safety Laboratory Tests**

| Laboratory Tests                | Parameters                                                                                                                                 |                                                                                          |                                                                    |                                                                                                                  |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Hematology                      | Platelet count                                                                                                                             | RBC indices:<br>Mean corpuscular volume<br>Mean corpuscular hemoglobin<br>%Reticulocytes |                                                                    | White blood cell count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
|                                 | Red blood cell (RBC) count                                                                                                                 |                                                                                          |                                                                    |                                                                                                                  |
|                                 | Hemoglobin                                                                                                                                 |                                                                                          |                                                                    |                                                                                                                  |
|                                 | Hematocrit                                                                                                                                 |                                                                                          |                                                                    |                                                                                                                  |
| Clinical chemistry <sup>1</sup> | Blood urea nitrogen                                                                                                                        | Potassium                                                                                | Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase | Total and direct bilirubin                                                                                       |
|                                 | Creatinine                                                                                                                                 | Sodium                                                                                   | Alanine aminotransferase/serum glutamic-pyruvic transaminase       | Total protein                                                                                                    |
|                                 | Glucose (non-fasting)                                                                                                                      | Calcium                                                                                  | Alkaline phosphatase <sup>2</sup>                                  | Serum electrolyte and glucose monitoring                                                                         |
| Thyroid function                | <ul style="list-style-type: none"> <li>• thyroid-stimulating hormone</li> <li>• free triiodothyronine</li> <li>• free thyroxine</li> </ul> |                                                                                          |                                                                    |                                                                                                                  |

| Laboratory Tests                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Parameters                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Routine urinalysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <ul style="list-style-type: none"> <li>• Specific gravity</li> <li>• pH, glucose, protein, blood, ketones, by dipstick</li> <li>• Microscopic examination (if blood or protein is abnormal)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Pregnancy testing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>• Highly sensitive serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) at screening<sup>3</sup></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Other screening tests                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <ul style="list-style-type: none"> <li>• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only)</li> <li>• Hepatitis B virus testing: hepatitis B surface antigen, hepatitis B surface antibodies, hepatitis B core antibodies, HBV DNA as outlined in <a href="#">Section 8.2.6.2</a></li> <li>• Hepatitis C virus antibody</li> <li>• Syphilis testing</li> <li>• Antinuclear antibody/anti-double-stranded DNA</li> <li>• Herpes Simplex virus (immunoglobulin M/immunoglobulin G)</li> <li>• Varicella Zoster (immunoglobulin M/immunoglobulin G)</li> <li>• Tuberculosis testing: QuantiFERON test or purified protein derivative (PPD) test               <ul style="list-style-type: none"> <li>○ Note: T-SPOT tuberculosis test may be acceptable if agreed upon with the medical monitor</li> </ul> </li> <li>• All study-required laboratory tests will be performed by a central laboratory, with the exception of:               <ul style="list-style-type: none"> <li>○ Urine pregnancy test</li> <li>○ QuantiFERON test (can be tested by a central lab or a local lab)</li> <li>○ PPD test</li> </ul> </li> </ul> |
| Other tests                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>• C-reactive protein</li> <li>• Pharmacokinetics</li> <li>• Anti-drug antibody</li> <li>• Hemoglobin A1c (HbA1c)</li> <li>• Human immunodeficiency virus (HIV)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p>NOTES:</p> <p><sup>1</sup> Details of liver chemistry stopping criteria and required actions and follow-up are given in <a href="#">Section 7.1.1</a> Liver Chemistry Stopping Criteria and <a href="#">Section 10.5</a> Liver Safety: Required Actions and Follow-up Assessments and Study drug/Rechallenge Guidelines.</p> <p><sup>2</sup> If alkaline phosphatase is elevated, consider fractionating.</p> <p><sup>3</sup> After screening, local urine pregnancy testing will be performed unless serum testing is required by local regulation, regulatory agency or Institutional Review Board/Independent Ethics Committee.</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Investigators must document their review of each laboratory safety report.

### 10.3. AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

#### 10.3.1. Definition of AE

| AE Definition                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug.</li> <li>NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of study drug.</li> </ul> |

| Events Meeting the AE Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Any abnormal laboratory test results (hematology, clinical chemistry or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease)</li> <li>Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition</li> <li>New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study</li> <li>Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction</li> <li>Signs, symptoms or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae</li> <li>Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE</li> </ul> |

| Events <u>NOT</u> Meeting the AE Definition                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition</li> <li>The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition</li> </ul> |

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

### 10.3.2. Definition of SAE

**An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:**

#### **a. Results in death**

#### **b. Is life-threatening**

The term *life-threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

#### **c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

#### **d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

#### **e. Is a congenital anomaly/birth defect**

**f. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of study drug dependency or study drug abuse.

**10.3.3. Recording and Follow-up of AE and/or SAE****AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the required CRF/SAE form.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee in lieu of completion of the required CRF/SAE form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, must be fully redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Severity**

The investigator will make an assessment of severity for each AE and SAE reported during the study according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0:

- **Mild (Grade 1):** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2):** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- **Severe (Grade 3):** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- **Life-threatening (Grade 4):** Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5):** Events that result in death.

Many common AEs are able to be graded according to CTCAE. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in CTCAE version 5.0 as stated above. Additional considerations when assessing severity are outlined below:

- The seriousness of an AE should not be confused with its severity. Severity is a measure of intensity (eg, Grades 1 through 5 or mild, moderate, severe), whereas seriousness is based on subject/event outcome as defined by the criteria in [Section 10.3.2](#).
- It is important to distinguish between category (AE versus SAE) and severity (Grades 1 to 5) of AEs. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.
- An AE of severe intensity is not necessarily considered serious. For example, nausea that persists for several hours may be considered grade 3 nausea, but not an SAE. On the other hand, minor cardiac chest pain that results in hospitalization may be considered grade 1 but would be an SAE.

### Assessment of Causality

The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The investigator will use clinical judgment in the assessment of causality according to the following categories:

- **Not related:** A causal relationship can be excluded, and another documented cause of the AE is most plausible
- **Related:** A causal relationship is clinically/biologically plausible and there exists a plausible time sequence between onset of the AE and administration of the study drug

Additional factors in the assessment of causality include the following:

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.

- The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

#### **Follow-up of AEs and SAEs**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

#### **10.3.4. Reporting of SAEs**

##### **SAE Reporting to Sponsor/Designee via the SAE Report Form**

- The primary mechanism for reporting an SAE to the sponsor/designee will be the SAE Report Form.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from investigator's knowledge of the event.
- Email transmission of the SAE Report Form is the preferred method to transmit this information to the sponsor/designee.

- In the rare circumstance email is not available, the SAE Report Form may be sent by facsimile as a backup reporting method.
- Investigator signature is required to be collected on the SAE Report Form prior to submission. With rare exception, the form may be sent without signature in order to meet the reporting deadline; however, investigator signature is required to be obtained as soon as possible after submission.
- Contacts for SAE reporting can be found on the SAE Report Form.

## 10.4. Contraceptive and Barrier Guidance

### 10.4.1. Definitions

#### Woman of Childbearing Potential

Women in the following categories are considered WOCBP (fertile):

- Following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 follicle-stimulating hormone measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

**Note:** Documentation can come from the site personnel's review of the subject's medical records, medical examination or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

**10.4.2. Contraception Guidance**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CONTRACEPTIVES<sup>a</sup> ALLOWED DURING THE STUDY INCLUDE:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Highly Effective Methods<sup>b</sup> that have Low User Dependency</b> <i>Failure rate of &lt; 1% per year when used consistently and correctly.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>• Implantable progestogen-only hormone contraception associated with inhibition of ovulation</li> <li>• Intrauterine device</li> <li>• Intrauterine hormone-releasing system</li> <li>• Bilateral tubal occlusion</li> <li>• Azoospermic partner (vasectomized or due to a medical cause)</li> </ul> <p><i>Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.</i></p> <p>Note: Documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination or medical history interview.</p> |
| <b>Highly Effective Methods<sup>b</sup> that are User Dependent</b> <i>Failure rate of &lt; 1% per year when used consistently and correctly.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation <ul style="list-style-type: none"> <li>–oral</li> <li>–intravaginal</li> <li>–transdermal</li> <li>–injectable</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Progestogen-only hormone contraception associated with inhibition of ovulation <ul style="list-style-type: none"> <li>–oral</li> <li>–injectable</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Sexual abstinence<br><i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Effective Methods<sup>c</sup> that are Not Considered Highly Effective</b> <i>Failure rate of <math>\geq</math> 1% per year when used consistently and correctly.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <ul style="list-style-type: none"> <li>• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action</li> <li>• Male or female condom with or without spermicide</li> <li>• Cervical cap, diaphragm or sponge with spermicide</li> <li>• A combination of male condom with either cervical cap, diaphragm or sponge with spermicide (double-barrier methods)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.<br>b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.<br>c) Considered effective, but not highly effective failure rate of $\geq$ 1% per year.<br>Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).                                                                                                           |

## 10.5. Liver Safety: Suggested Actions and Follow-up Assessments and Study Drug Restart/Rechallenge Guidelines

Phase 2 liver chemistry stopping criteria are designed to assure subject safety and to evaluate liver event etiology. The guidelines provided below are based on the European Association for the Study of the Liver Clinical Practice Guidelines: Drug-induced Liver Injury (2019) and Food and Drug Administration 2009 Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation.

### Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

| Liver Chemistry Stopping Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ALT or AST Absolute</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | ALT or AST $\geq 5 \times$ ULN                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>ALT or AST Increase</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | ALT or AST $\geq 3 \times$ ULN persists for $\geq 4$ weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Bilirubin<sup>1,2</sup></b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | ALT or AST $\geq 3 \times$ ULN <b>and</b> total bilirubin $\geq 2 \times$ ULN ( $> 35\%$ direct bilirubin)                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>International Normalized Ratio (INR)<sup>2</sup></b>                                                                                                                                                                                                                                                                                                                                                                                                                                            | ALT or AST $\geq 3 \times$ ULN <b>and</b> INR $> 1.5$                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Cannot Monitor</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | ALT or AST $\geq 3 \times$ ULN and cannot be monitored twice weekly for 4 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Symptomatic<sup>3</sup></b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | ALT or AST $\geq 3 \times$ ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity                                                                                                                                                                                                                                                                                                                                                                                  |
| Suggested Actions, Monitoring and Follow-up Assessments                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Follow-up Assessments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <ul style="list-style-type: none"> <li>• <b>Immediately</b> discontinue study drug.</li> <li>• Report the event to the sponsor/designee <b>within 24 hours</b>.</li> <li>• Complete a serious adverse event (SAE) CRF if the event met the criteria for an SAE.<sup>2</sup></li> <li>• Perform follow-up assessments as described in the Follow-up Assessment column.</li> <li>• Monitor the subject until liver chemistry test abnormalities resolve, stabilize or return to baseline.</li> </ul> | <ul style="list-style-type: none"> <li>• Viral hepatitis serology.<sup>3</sup></li> <li>• Obtain blood samples for pharmacokinetic (PK) analysis after the most recent dose.<sup>4</sup></li> <li>• Obtain serum creatine phosphokinase, lactate dehydrogenase, gamma-glutamyltransferase, glutamate dehydrogenase and serum albumin.</li> <li>• Fractionate bilirubin, if total bilirubin <math>\geq 2 \times</math> ULN.</li> <li>• Obtain complete blood count with differential to assess eosinophilia.</li> </ul> |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>MONITORING:</b></p> <p><b>If ALT or AST <math>\geq 3 \times</math> ULN AND total bilirubin <math>\geq 2 \times</math> ULN or INR <math>&gt; 1.5</math>:</b></p> <ul style="list-style-type: none"> <li>• Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within <b>24 hours</b>.</li> <li>• Monitor subject twice weekly until liver chemistry test abnormalities resolve, stabilize or return to baseline.</li> <li>• A hepatology consultation is recommended.</li> </ul> <p><b>If ALT or AST <math>\geq 3 \times</math> ULN AND total bilirubin <math>&lt; 2 \times</math> ULN and INR <math>\leq 1.5</math>:</b></p> <ul style="list-style-type: none"> <li>• Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver chemistry follow-up assessments within <b>24 to 72 hours</b>.</li> <li>• Monitor subjects weekly until liver chemistry abnormalities resolve, stabilize or return to baseline.</li> <li>• <b>Do not restart/rechallenge</b> subject with study drug unless allowed per protocol and sponsor approval is granted.</li> </ul> | <ul style="list-style-type: none"> <li>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the CRF.</li> <li>• Record use of concomitant medications (including acetaminophen, herbal remedies and other over-the-counter medications) on the concomitant medications CRF.</li> <li>• Record alcohol use on the liver event alcohol intake form.</li> </ul> <p><b>If ALT or AST <math>\geq 3 \times</math> ULN AND total bilirubin <math>\geq 2 \times</math> ULN or INR <math>&gt; 1.5</math>, obtain the following in addition to the assessments listed above:</b></p> <ul style="list-style-type: none"> <li>• Antinuclear antibody, antismooth muscle antibody, type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G or gamma globulins</li> <li>• Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week</li> <li>• Liver imaging (ultrasound, magnetic resonance or computerized tomography) to evaluate liver disease</li> <li>• Liver biopsy may be considered and discussed with local specialist if available, for instance: <ul style="list-style-type: none"> <li>○ In subjects when serology raises the possibility of autoimmune hepatitis</li> <li>○ In subjects when suspected drug-induced liver injury progresses or fails to resolve on withdrawal of study drug</li> </ul> </li> </ul> |
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|  |                                                                                                                                                                              |
|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <ul style="list-style-type: none"> <li>○ In subjects with acute or chronic atypical presentation</li> <li>● If liver biopsy conducted provides biopsy information</li> </ul> |
|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

ALT = alanine transaminase; AST = aspartate transaminase; CRF = case report form; INR = international normalized ratio; ULN = upper limit of normal

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT or AST  $\geq 3 \times \text{ULN}$  **and** total bilirubin  $\geq 2 \times \text{ULN}$  ( $> 35\%$  direct bilirubin) or ALT or AST  $\geq 3 \times \text{ULN}$  **and** INR  $> 1.5$  may indicate severe liver injury (**possible ‘Hy’s Law’**) **and must be reported to the sponsor in an expedited manner and as an SAE if SAE criteria are met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study drug prior to the blood sample draw on the CRF. If the date/time of the last dose is unclear, provide the subject’s best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Laboratory Manual.

**10.6. Abbreviations and Definitions**

| <b>Abbreviation</b> | <b>Definition</b>                                                |
|---------------------|------------------------------------------------------------------|
| ACC                 | anterior chamber cell                                            |
| ADA                 | anti-drug antibody                                               |
| ADL                 | activities of daily living                                       |
| AE                  | adverse event                                                    |
| ANA                 | antinuclear antibody                                             |
| AREDS               | Age-Related Eye Disease Study                                    |
| AUC                 | area under the concentration-time curve                          |
| AUC <sub>0-τ</sub>  | area under the concentration-time curve over the dose interval   |
| AUC <sub>0-∞</sub>  | area under the concentration-time curve extrapolated to infinity |
| BCVA                | best corrected visual acuity                                     |
| C <sub>max</sub>    | maximum observed plasma concentration                            |
| COVID-19            | coronavirus disease of 2019                                      |
| CRF                 | case report form                                                 |
| CRO                 | Contract Research Organization                                   |
| CRT                 | central retinal thickness                                        |
| CTCAE               | Common Terminology Criteria for Adverse Events                   |
| CV%                 | percent coefficient of variation                                 |
| DMC                 | Data Monitoring Committee                                        |
| ECG                 | electrocardiogram                                                |
| CCI                 |                                                                  |
| ETDRS               | Early Treatment Diabetic Retinopathy Study                       |
| EudraCT             | European Union Drug Regulating Authorities Clinical Trials       |
| FA                  | fluorescein angiography                                          |
| GCP                 | Good Clinical Practice                                           |
| HBcAb               | hepatitis B core antibody                                        |
| HBsAb               | hepatitis B surface antibody                                     |
| HBsAg               | hepatitis B surface antigen                                      |
| HBV                 | hepatitis B virus                                                |
| HIV                 | human immunodeficiency virus                                     |
| HRT                 | hormonal replacement therapy                                     |
| IBD                 | inflammatory bowel disease                                       |
| ICEs                | intercurrent events                                              |

| Abbreviation  | Definition                                        |
|---------------|---------------------------------------------------|
| ICH           | International Council for Harmonisation           |
| ICF           | informed consent form                             |
| IEC           | Independent Ethics Committee                      |
| IL            | interleukin                                       |
| IRB           | Institutional Review Board                        |
| IXRS          | Interactive Response Technology                   |
| IV            | intravenous(ly)                                   |
| MDRD          | Modification of Diet in Renal Disease             |
| MMRM          | mixed effects model with repeated measures        |
| NEI           | National Eye Institute                            |
| NOAEL         | no observed adverse effect level                  |
| NRI           | non-response imputation                           |
| PASI90        | Psoriasis Area and Severity Index response of 90% |
| PCR           | polymerase chain reaction                         |
| PK            | pharmacokinetic(s)                                |
| PPD           | purified protein derivative                       |
| Q2W           | every 2 weeks                                     |
| QW            | once weekly                                       |
| SAE           | serious adverse event                             |
| SARS-CoV-2    | severe acute respiratory syndrome coronavirus     |
| SC            | subcutaneous(ly)                                  |
| SD-OCT        | Spectral-Domain Optical Coherence Tomography      |
| CCI           |                                                   |
| SoA           | Schedule of Activities                            |
| SUN           | Standardization of Uveitis Nomenclature           |
| SUSAR         | suspected unexpected serious adverse reaction     |
| $t_{1/2}$     | half-life                                         |
| TB            | tuberculosis                                      |
| TEAE          | treatment-emergent adverse event                  |
| Th            | T-helper                                          |
| $t_{max}$     | time to maximum observed concentration            |
| TNF- $\alpha$ | tumor necrosis factor-alpha                       |
| US            | United States                                     |

| Abbreviation | Definition                         |
|--------------|------------------------------------|
| VEGF         | vascular endothelial growth factor |
| VFQ-25       | Visual Function Questionnaire-25   |
| WOCBP        | women of childbearing potential    |

### 10.7. Corticosteroid Equivalent Doses

| Product Name       | Dose Equivalent to Prednisone/Prednisolone |        |         |         |        |        |        |
|--------------------|--------------------------------------------|--------|---------|---------|--------|--------|--------|
|                    | 5 mg                                       | 10 mg  | 12 mg   | 15 mg   | 20 mg  | 30 mg  | 40 mg  |
| Betamethasone      | 0.75 mg                                    | 1.5 mg | 1.8 mg  | 2.25 mg | 3 mg   | 4.5 mg | 6 mg   |
| Cortisone          | 25 mg                                      | 50 mg  | 60 mg   | 75 mg   | 100 mg | 150 mg | 200 mg |
| Deflazacort        | 6 mg                                       | 12 mg  | 14.4 mg | 18 mg   | 24 mg  | 36 mg  | 38 mg  |
| Dexamethasone      | 0.75 mg                                    | 1.5 mg | 1.8 mg  | 2.25 mg | 3 mg   | 4.5 mg | 6 mg   |
| Hydrocortisone     | 20 mg                                      | 40 mg  | 48 mg   | 60 mg   | 80 mg  | 120 mg | 160 mg |
| Methylprednisolone | 4 mg                                       | 8 mg   | 9.6 mg  | 12 mg   | 16 mg  | 24 mg  | 32 mg  |
| Paramethasone      | 2 mg                                       | 4 mg   | 4.8 mg  | 6 mg    | 8 mg   | 12 mg  | 16 mg  |
| Triamcinolone      | 4 mg                                       | 8 mg   | 9.6 mg  | 12 mg   | 16 mg  | 24 mg  | 32 mg  |

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