KZR-616-208

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2A STUDY WITH OPEN-LABEL EXTENSION TO EVALUATE THE SAFETY AND EFFICACY OF ZETOMIPZOMIB (KZR-616) IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Clinicaltrials.gov Identifier	*NCT05569759*
Date of protocol:	*26 February 2024*

CLINICAL STUDY PROTOCOL

Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Phase 2a Study with Open-label Extension to Evaluate the Safety and Efficacy of Zetomipzomib (KZR-616) in Patients with Autoimmune Hepatitis
Protocol Number:	KZR-616-208
Investigational Medicinal Product:	Zetomipzomib (KZR-616)
Indication:	Autoimmune hepatitis (AIH)
Development Phase:	2a
[redacted]	[redacted]
Sponsor:	Kezar Life Sciences, Inc. 4000 Shoreline Court, Suite 300 South San Francisco, CA 94080 Telephone: 650-822-5600
Protocol Version and Date:	Version 4.0, 26 February 2024 Version 3.0, 07 March 2023 Version 2.0, 15 September 2022 Version 1.0, 22 July 2022

Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

STUDY PERSONNEL

Serious Adverse Event Reporting Details (to be used for submitting SAE forms and Pregnancy Report Form):

[redacted]

Central Safety Fax: [redacted]

* = country exit code

Kezar/Clinical Study Lead

Name	[redacted]
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Medical Monitor

Name	[redacted]
Title	Medical Monitor
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Serious Adverse Event Reporting Contact

[redacted] **Safety Lead**

Name	[redacted]
Title	Senior Project Manager
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PROTOCOL ACCEPTANCE PAGE

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the International Council for Harmonisation Guideline (ICH) for Good Clinical Practice (GCP), the Declaration of Helsinki, all local, regional, and national regulatory requirements (including the Code of Federal Regulations [CFR] Title 21 for US Investigators), requirements of the applicable Institutional Review Board/Independent Ethics Committee, and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines, to appropriately direct and assist the staff under my control that will be involved in the trial and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator Name: _____

Name of Institution/Site: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

NAME OF INVESTIGATIONAL PRODUCT:
zetomipzomib (KZR-616)

NAME OF ACTIVE INGREDIENT:
zetomipzomib (KZR-616) maleate

CLINICAL CONDITION(S)/INDICATION(S)

Autoimmune hepatitis (AIH)

PROTOCOL NUMBER: KZR-616-208

PROTOCOL TITLE:

A Randomized, Double-blind, Placebo-controlled, Phase 2a Study with Open-Label Extension to Evaluate the Safety and Efficacy of Zetomipzomib (KZR-616) in Patients with Autoimmune Hepatitis

SHORT TITLE: Safety and Efficacy of Zetomipzomib (KZR-616) for Autoimmune Hepatitis

STUDY PHASE: Phase 2a

STUDY OBJECTIVES:

Safety: To evaluate the safety and tolerability of zetomipzomib (KZR-616) in patients with autoimmune hepatitis (AIH).

Efficacy: The efficacy objective for the Double-blind Treatment Period is to evaluate the efficacy of zetomipzomib in addition to standard-of-care in patients with AIH who have failed standard-of-care treatment, had an incomplete biochemical response to ≥3 months of standard-of-care treatment, or had a disease flare after experiencing complete remission induced by standard-of-care treatment. The efficacy objective for the OLE Period is to evaluate the long-term efficacy of zetomipzomib in patients with AIH.

STUDY DESIGN:

This is a Phase 2a, multi-center, randomized, double-blind, placebo-controlled study with an open-label extension to evaluate the safety, tolerability, and efficacy of zetomipzomib in patients with AIH who have failed standard-of-care treatment, had an incomplete biochemical response to ≥3 months of standard-of-care treatment, or had a disease flare after experiencing complete remission induced by standard-of-care treatment.

Double-blind Treatment Period

In the Double-blind Treatment Period, zetomipzomib or placebo will be administered weekly for a 24-week treatment period. A screening period of up to 4 weeks will precede Day 1. Efficacy will be assessed at Weeks 12, 16, 20, and 24; assessments are discussed in Section 7.2.2. Safety will be assessed throughout the study by monitoring of vital signs, clinical laboratory tests, and physical examinations, and by recording and analyzing all adverse events (AEs) and serious AEs (SAEs).

Eligible patients will be randomized in a 2:1 ratio on Day 1 (Visit 2) to receive either standard-of-care (glucocorticoids) with zetomipzomib (Active Treatment group), or standard-of-care with Placebo (Control group). Zetomipzomib and placebo (ie, sterile water for injection [WFI] in an equivalent volume to the reconstituted zetomipzomib dose), will be administered subcutaneously (SC) once weekly by study personnel at the site or by a home trial service at the patient's home or alternate location (eg, place of employment). The first dose of investigational medicinal product (IMP) will be 30 mg zetomipzomib or placebo, followed by weekly doses of 60 mg zetomipzomib or placebo for the remaining 23 weeks of the Double-blind Treatment Period.

Enrolled patients will be on standard-of-care with a prednisone/prednisone equivalent dose of 20 mg/day on Day 1 (Visit 2). Following consultation with the Medical Monitor, patients who are taking a prednisone/prednisone equivalent dose higher than 20 mg/day at Baseline may also be enrolled in the study provided the prednisone/prednisone equivalent dose does not exceed 40 mg/day. Patients are encouraged to undergo a glucocorticoid taper of prednisone/prednisone equivalent dose according to the protocol-suggested glucocorticoid taper schedule (Table 6) and prednisone equivalent doses (Table 7) as provided in Appendix B. Patients taking budesonide who are unwilling to switch to a prednisone/prednisone equivalent for the study may continue to take budesonide at the doses shown in Appendix B. For suggested glucocorticoid taper schedule, please see Appendix B.

In addition to prednisone/prednisone equivalent, patients may continue to use up to two additional immunosuppressive agents if these agents are already used as baseline therapy:

a) Oral azathioprine (AZA) *or* oral mycophenolate mofetil (MMF; including the alternatives mycophenolate sodium [MMS] or mycophenolic acid [MPA])
and/or

b) Oral tacrolimus (TAC), cyclosporine A (CsA), *or* 6-mercaptopurine (6-MP)

The dose of these immunosuppressants must be stable for at least 4 weeks prior to Screening and must be held constant unless tolerability/AEs require dose adjustment and glucocorticoid taper is completed. Following completion of the glucocorticoid taper, immunosuppressants may be decreased at the Investigator's discretion (Section 6.2.3).

During the glucocorticoid taper, patients with signs and symptoms of worsening disease (ie, worsening of alanine aminotransferase [ALT] level ≥25% from Baseline for ≥1 week, as verified via repeat laboratory assessments) may increase glucocorticoid doses following consultation with the Medical Monitor.

For patients who are confirmed treatment failures or who experience a disease flare (see Section 2.2.2) during the treatment period, IMP may be discontinued upon consultation with the Medical Monitor, and additional care will be introduced as medically indicated. Patients who receive rescue therapy (see Section 6.3) will temporarily discontinue IMP, complete the Double-blind Period visits, and remain eligible for the OLE Period. Patients who do not receive rescue therapy but undergo a temporary interruption in IMP (≤2 consecutive doses or ≤4 total doses) should also remain in the study. Patients who discontinue participation in the study due to a disease flare will be considered treatment failures. If the patient cannot continue with the planned assessments, the patient will complete the Early Termination Visit (ETV; Table 3) followed by the End-of-Study (EOS) visit (Table 3) 4 weeks later.

Patients who are eligible to roll over to the OLE Period will receive their first SC injection of zetomipzomib at the dose and schedule described in the OLE Period section. Patients who are not eligible or choose not to roll over to the OLE Period will have an End-of-Study (EOS) visit (see Table 3) 4 weeks after completion of the Double-blind Treatment Period.

A liver biopsy will be performed at the Week 24 visit to assess changes from Baseline in liver histopathology.

Open-label Extension (OLE) Period

Patients who complete the Double-blind Period study visits through Week 24 are eligible to roll over to the OLE Period. If a patient does not meet eligibility criteria for the OLE Period, then the patient would proceed with the EOS visit. The patient would not be considered a screen fail for the OLE Period.

All patients will receive a SC injection of 30 mg zetomipzomib at the OLE Week 1 visit, followed by weekly SC injections of 60 mg zetomipzomib, administered by study personnel at the site or by a home trial service at the patient's home or alternate location (eg, place of employment), for a total of 24 additional weeks of treatment. After the OLE Week 1 Visit, additional on-site study visits will occur at least every 4 weeks from OLE Week 4 through OLE Week 20. An additional on-site visit will occur at OLE Week 25 (End-of-Treatment [EOT] visit). At these visits, safety and efficacy assessments will be performed. Patients will have a safety follow-up visit (EOS Visit) 4 weeks after their last dose of zetomipzomib, for a maximum potential length of participation in the OLE of 28 weeks.

During the course of the OLE Period, prednisone/prednisone equivalent can continue to be tapered and may be withdrawn (see Appendix B for suggested taper schedule). Patients with signs and symptoms of worsening disease (ie, worsening of ALT level ≥25% from OLE Baseline for ≥1 week, as verified via repeat laboratory assessments) may increase glucocorticoid doses following consultation with the Medical Monitor. For patients who are confirmed treatment failures or who experience a disease flare (see Section 2.2.2) during the OLE Treatment Period, IMP may be discontinued upon consultation with the Medical Monitor, and additional care will be introduced as medically indicated. Patients who receive rescue therapy (see Section 6.3) will temporarily discontinue IMP but will remain in the study to complete OLE visits. Patients who do not receive rescue therapy but undergo a temporary interruption in IMP (≤2 consecutive doses or ≤4 total doses) should also remain in the study. Patients who discontinue participation in the study due to a disease flare will be considered treatment failures. If the patient cannot continue with the planned assessments, the patient will complete the ETV (Table 3) followed by the End-of-Study (EOS) visit (Table 3) 4 weeks later.

An optional liver biopsy may be performed at the OLE Week 25 visit to assess changes in liver histopathology.

The overall study design is shown in Figure 1.

Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will review safety findings after data are available from the Double-blind Treatment Period Week 12 visit for 6, 12, 18, and 24 patients. After all patients have completed at least 12 weeks of treatment or have withdrawn early, the IDMC will continue to review safety data every 3 to 6 months until the last patient completes the study.

ENDPOINTS:

Definitions related to study endpoints (eg, complete remission, partial remission, disease flare, etc.) can be found in Section 2.2.2.

Safety Endpoints:

The primary safety endpoint is the proportion of patients who experience AEs and SAEs. Other safety endpoints include:

- Incidence, nature, and severity of AEs and SAEs
- Incidence of AEs leading to IMP discontinuation and dose reduction
- Changes in standard laboratory parameters, vital signs, and ECGs

Efficacy Endpoints:

Double-blind Treatment Period

Primary Efficacy Endpoint

- Proportion of patients who achieve complete remission (CR) by Week 24; analyses will also be performed on data collected at Weeks 12, 16, and 20

Secondary Efficacy Endpoints

- Changes from Baseline in ALT at Weeks 12, 16, 20, and 24
- Proportion of patients who achieve partial remission (PR) at Week 12, 16, 20, and 24
- Time to CR
- Time to PR
- Proportion of patients experiencing a disease flare after CR
- Proportion of patients who are treatment failures
- Proportion of patients who achieve CR or PR with successful glucocorticoid taper by Week 24; analyses will also be performed on data collected at Weeks 12, 16, and 20

Exploratory Efficacy Endpoints:

- Proportion of patients who achieve ALT normalization based on Prati criteria (males, 30 U/L; females, 19 U/L) (Prati et al., 2002), with successful glucocorticoid taper, by Week 24
- Mean changes from Baseline in aspartate aminotransferase (AST) at Weeks 12, 16, 20, and 24
- Mean changes from Baseline in immunoglobulin G (IgG) at Weeks 12, 16, 20, and 24
- Mean changes from Baseline in glucocorticoid dose
- Change from Baseline in the Glucocorticoid Toxicity Index (GTI) Cumulative Worsening Score (GTI-CWS) and the Aggregate Improvement Score (GTI-AIS)
- Mean changes from Baseline in inflammatory cytokines at Weeks 8, 16, and 24
- Change from Baseline in liver stiffness at Week 24, assessed by vibration-controlled transient elastography (VCTE) utilizing Fibroscan®
- Mean change from Baseline in the EuroQol 5-dimension 5-level (EQ-5D-5L) at Weeks 16 and 24
- Mean change from Baseline in Chronic Liver Disease Questionnaire (CLDQ) at Weeks 16 and 24
- Change from Baseline in liver histopathology at Week 24, based on Ishak score (modified Histological Activity Index HAI]) scores (Ishak et al., 1995)

Open-label Extension

Primary Efficacy Endpoints

- Proportion of patients experiencing a disease flare among the patients who achieved a CR during the Double-blind Treatment Period

Exploratory Efficacy Endpoints

- Proportion of patients who have a CR or PR among the patients who did not achieve a CR or PR during the Double-blind Treatment Period
- Proportion of patients who have a CR or PR with successful glucocorticoid taper who did not achieve a CR or PR during Double-blind Treatment Period
- Proportion of patients who achieve a glucocorticoid-free CR
- Proportion of patients who achieve a glucocorticoid-free PR
- Mean changes in ALT
- Mean changes in AST
- Mean changes in IgG
- Mean change in the EQ-5D-5L
- Mean change in CLDQ
- Change in the GTI-CWS and the GTI-AIS
- Mean change in liver stiffness, assessed by VCTE utilizing Fibroscan®
- Change in liver histopathology, based on Ishak score (modified HAI) scores (Ishak et al., 1995)

Pharmacokinetic Endpoints:

- Zetomipzomib and its metabolite KZR-59587 pharmacokinetics (PK) (maximum concentration [C_{max}], time of maximum concentration [T_{max}], area under the concentration-time curve [AUC])

INVESTIGATIONAL PRODUCT(S), DOSE, AND MODE OF ADMINISTRATION:

Investigational Medicinal Product: IMPs include zetomipzomib and placebo control. Placebo control will consist of sterile WFI in an equivalent volume to the reconstituted zetomipzomib dose. Instructions for the receipt, inspection, storage, preparation, administration, and disposal of IMP will be provided in a separate Pharmacy Manual.

Dose and Dose Frequency: An unblinded Pharmacist will prepare and blind the active and placebo doses. During the Double-blind Treatment Period, IMP will be administered by SC injection once weekly, according to randomization. The first dose will be 30 mg zetomipzomib or placebo, administered at the clinical trial site, followed by weekly doses of 60 mg zetomipzomib or placebo for the remaining 23 weeks of the Double-blind Treatment Period. During the OLE Period, zetomipzomib will be administered to all patients by SC injection once weekly. The first open-label dose will be 30 mg zetomipzomib, followed by weekly doses of 60 mg zetomipzomib for the duration of the OLE Period.

After the first dose, IMP will be administered by study personnel at the site or by a home trial service at the patient's home or alternate location (eg, place of employment). Doses will be administered according to the Schedules of Assessments (Table 1 through Table 4).

Background Medication:

Patients will take their own supply of glucocorticoids. Enrolled patients will be on standard-of-care with a prednisone/prednisone equivalent dose of 20 mg/day on Day 1 (Visit 2). Following consultation with the Medical Monitor, patients who are taking a prednisone/prednisone equivalent dose higher than 20 mg/day at Day 1 may also be enrolled in the study provided the prednisone/prednisone equivalent dose does not exceed 40 mg/day. The prednisone equivalents are outlined in Appendix B.

In addition to prednisone/prednisone equivalent, patients may continue to use up to two additional immunosuppressive agents if these agents are already used as baseline therapy:

a) Oral AZA *or* oral MMF (including the alternatives MMS or MPA)
and/or
b) Oral TAC, CsA, *or* 6-MP

The dose of these immunosuppressants must be stable for at least 4 weeks prior to Screening and must be held constant unless tolerability/AEs require dose adjustment and glucocorticoid taper is completed. Following completion of the glucocorticoid taper, immunosuppressants may be decreased at the Investigator's discretion (Section 6.2.3).

PATIENT SELECTION:

Targeted Number of Patients: Approximately 24 patients (randomized in a 2:1 ratio; Active Treatment group: Control group)

Planned Number of Sites: Up to 24 sites

Inclusion Criteria:

Double-blind Treatment Period

1. Must be aged ≥18 years.
2. Must have a clinical diagnosis of AIH and signs of active disease despite standard-of-care therapy for ≥3 months or disease flare after experiencing complete remission induced by standard-of-care treatment, including:
    a. Screening ALT values that are 1.25 to 10 times the upper limit of normal (ULN)
    b. Liver biopsy results with Ishak score (modified HAI) ≥5/18 (Ishak et al., 1995) indicating active AIH, from a biopsy performed at Screening or within 6 months prior to Screening
    c. Mild or no hepatic impairment (Child-Pugh category A)
3. Must be willing to use and taper glucocorticoid therapy as described in Section 3.1 and Section 6.2.2.1.
4. Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test prior to the first dose of IMP in Study KZR-616-208 and must agree to continue to use a highly effective method of birth control until completion of the study (or 30 days following the last dose of IMP in case of early withdrawal). For the purposes of this study, WOCBP are defined as fertile female patients, unless the patient is postmenopausal (defined by amenorrhea for at least 2 years or amenorrhea for at least 1 year with confirmatory follicle stimulating hormone [FSH] level in the postmenopausal range, as documented historically or measured by the central or local laboratory and if patient is not on supplementary hormonal therapy) or surgically sterile (ie, tubal ligation, hysterectomy, bilateral salpingo-ophorectomy).
5. Male patients must agree to use an effective contraception method (eg, condom with spermicide) during the study, and continue to use this method for 1 week following their last dose of IMP or be congenitally or surgically sterile (eg, vasectomy with documented confirmation of post-surgical aspermia).
6. Must be willing and able to return for all protocol-specified clinic visits and complete all study-required procedures.

Open-label Extension Period

7. Same as Double-blind Treatment Period Inclusion criteria, except the following modifications to Inclusion Criterion 2:
    a. ALT value can be normal or, if elevated, in the range of 1.25 to 10 times the ULN
    b. Inclusion Criterion 2b does not apply to the OLE Period
    c. Inclusion Criterion 2c must be met
8. Must have completed the Double-blind Period study visits through Week 24, including all Week 24 Visit assessments.
9. Must be willing to maintain glucocorticoid therapy or continue to taper glucocorticoid therapy as described in Section 6.2.2.1.

Exclusion Criteria:

Double-blind Treatment Period

1. Have a concomitant diagnosis of primary biliary sclerosis, primary sclerosing cholangitis, IgG 4-related cholangitis, drug-related AIH (at Screening) or a history of drug-related AIH.
2. Have clinical evidence of significant unstable or uncontrolled diseases other than the disease under study (eg, cardiac [including congestive heart failure, hypertension, angina, or myocardial infarction], pulmonary [including pulmonary hypertension or interstitial lung disease], hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurological, or infectious disease, any ongoing SAE(s), or AE(s) ≥ Grade 3 by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) that, in the opinion of the Investigator or Sponsor/designee, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence.

3. Are receiving oral or injectable immunomodulating treatment other than permitted concomitant medications in Section 6.2.3 prior to enrollment in the study. Patients who have been using such treatments must have had the washout periods outlined in Section 6.2.1.
4. Have an active infection (eg, acute hepatitis E, cytomegalovirus, or Epstein-Barr virus) requiring systemic therapy with antibiotic, antiviral, or antifungal treatment, or has had any febrile illness within 7 days prior to Day -1.
5. Have a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test (real-time polymerase chain reaction [RT-PCR]) at Screening or Day 1.
6. Have a history of thyroiditis, celiac disease, or other autoimmune disorder known to be associated with transaminitis.
7. Have a history of primary or acquired immunodeficiency.
8. Have a history of malignancy of any type, with the exceptions of surgically excised nonmelanoma skin cancers, in situ cervical cancer >5 years prior to Baseline (Day 1), prostate cancer that is considered cured (normal prostate-specific antigen) for >5 years, colon cancer considered cured >5 years following surgical treatment, or lymphoma with >5 years complete remission.
9. Have a history of solid organ transplant.
10. Have a history of excessive alcohol use (consumption of 4 or more drinks on any day or 8 or more drinks per week for women and 5 or more drinks on any day or 15 or more drinks per week for men) or drug abuse in the 1 year prior to Screening, in the opinion of the Investigator.
11. Have an estimated glomerular filtration rate <60 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease (MDRD) equation (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]).
12. Have a hemoglobin level <9.0 g/dL, neutrophil count <1200/mm^3, or platelet count <120 × 10^9/L at Screening.
13. Have a prothrombin time above ULN at Screening, or an International Normalized Ratio (INR) >1.2. NOTE: Minor changes in prothrombin time that may be attributable to permitted concomitant medications and that are not considered clinically significant by the Investigator are allowed.
14. Have a history of hypercoagulability (including, but not limited to, antiphospholipid antibody syndrome, activated protein C resistance, elevated coagulation factor VIII levels, sticky platelet syndrome, protein C or S deficiency, homocystinemia, antithrombin deficiency, dysfibrinolysis, or prothrombin G20210A mutation), thrombotic events (including, but not limited to, deep vein, femoral vein, superior vena cava, or jugular vein thrombosis; thrombotic stroke; pulmonary embolism; myocardial infarction; retinal vein occlusion, or thrombotic microangiopathies), or hemolytic uremic syndrome.
15. Have liver cirrhosis with significant impairment of liver function (Child Pugh category B or C) or have decompensated cirrhosis.
16. Patients with histology confirmed coincident non-alcoholic steatohepatitis. NOTE: Patients with other type of non-alcoholic fatty liver disease are NOT excluded from the study.
17. Have electrocardiogram (ECG) findings of QT corrected for pulse rate (QTcF)>480 msec, newly diagnosed (within 6 months prior to Screening) and/or poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant cardiac abnormalities.
18. Have positive serology results at Screening (human immunodeficiency virus [HIV], hepatitis B [surface antigen and core antibodies], hepatitis C [anti-HCV antibody confirmed with hepatitis C RNA]).
    - Patients who are hepatitis B virus surface antigen (HBsAg) positive will not be eligible.
    - Patients who are HBsAg negative and hepatitis B core antigen antibody (HBcAb) positive will be tested for hepatitis B surface antibody (HBsAb) and hepatitis B DNA:
      – Patients with HBsAb titer ≥100 IU/L and negative hepatitis B DNA may be enrolled.
      – Patients with positive hepatitis B DNA results will be excluded.
      – Patients with HBsAb titer <100 IU/L or negative will be excluded.

19. Have positive interferon-gamma release assay (IGRA) (eg, T-SPOT tuberculosis [TB] Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus), at Screening, unless the patient has latent TB and all of the following conditions are true:
    - The chest X-ray does not show evidence suggestive of active TB.
    - There are no clinical signs or symptoms of pulmonary and/or extra-pulmonary TB.
    - The patient has documented evidence of receiving one of the following prophylactic treatment regimens: daily oral isoniazid for 6 months, daily oral rifampin for 6 months, or isoniazid and rifapentine weekly for 3 months.

      Note: If a QuantiFERON®-TB Gold/Gold Plus is indeterminate for any reason and a T-SPOT TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor. On a case-by-case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to one of the above tests may be used for eligibility. Without a negative test, unless treated as noted above, one or more indeterminant tests are not sufficient for the patient to be enrolled (see Section 7.2.4.5.1.1).
20. Have taken rituximab, other B- or T-cell depleting agents, or alkylating agents within 6 months of Screening, unless B- or T-cells have been shown to return to normal values (B-cells [CD19+] >100 cells/μL; T-cells [CD4+] >500 cells/mm^3 [0.64 × 10^9/L]).
21. Require regular use of medications with known hepatotoxicity (see Section 6.2).
22. Have previously used a proteasome inhibitor (dual proteasome inhibitors allowed if it has been at least 1 year since last use).
23. Have received a live vaccine within 28 days prior to Baseline (Day 1), or plan to receive a live vaccine during the study.
24. Have used another investigational medical therapy, and/or participated in an investigational trial within 6 months or 5 half-lives (whichever is longer) prior to Screening.
25. Are females who are breastfeeding or who plan to become pregnant during the study, or who are actively trying to conceive at the time of signing of the informed consent form (ICF).
26. Have known hypersensitivity to zetomipzomib or any of its excipients.

Open-label Extension Period

27. Same as the Double-blind Treatment Period exclusion criteria. No need to re-test for HIV, HBV, HCV, and TB.

Patients who do not meet inclusion/exclusion criteria may be rescreened one time.

Pharmacokinetic Analysis:

Blood samples for determination of PK parameters (C_{max}, T_{max}, AUC) for zetomipzomib and its metabolite KZR-59587 will be collected from all patients during the Double-blind Treatment Period according to the Schedule of Assessments (Table 1).

STATISTICAL ANALYSIS:

The statistical analyses of the study data will be descriptive in nature, and no formal hypothesis testing will be performed. No formal statistical sample size or power estimation has been performed. The sample size of approximately 24 patients was set to allow a preliminary assessment of the potential effect of zetomipzomib with a glucocorticoid, and glucocorticoid treatment with placebo, in patients diagnosed with AIH. For example, a sample size of 16 patients (in the Active Treatment group) would have a two-sided 90% confidence interval (CI) with a half width of 0.188 (0.112–0.488), assuming a sample proportion of 0.30 (corresponding to efficacy and/or safety measure). This is a signal-seeking study designed to collect data and perform preliminary assessments on safety and efficacy endpoints between treatment groups.

No interim analyses are planned for this study. The first planned unblinded analysis of the data will be conducted after all patients have completed or would have completed the Week 24 visit or EOS visit, whichever occurs later, in the Double-blind Treatment Period, data being fully cleaned and database being “soft” locked to limit changes. The final data analysis will be conducted after all patients have completed the study (Double-blind Treatment Period and OLE Period).

Patient baseline characteristics, the primary and secondary endpoints, including efficacy, PK, and safety measures, will be summarized using simple descriptive statistics. A between-treatment difference value in an efficacy endpoint (primary or secondary) will be summarized using a point estimate and a two-sided 95% CI. Statistical uncertainty with regard to the efficacy outcome estimate will be presented in a two-sided 95% CI. Change scores from Baseline to follow-up visits (ie, Weeks 12, 14, 16, 24, or OLE visits) on the continuous secondary outcome parameters may be analyzed using the Wilcoxon signed rank test. Two-sided p-values may be calculated to help assess strength of evidence. Due to the explorative nature of this study, no adjustments (in p-values) will be applied to perform multiple comparisons.

Analysis Sets:

Full Analysis Set (FAS): The FAS for summaries of efficacy endpoints will include all randomized patients who receive at least 1 dose of IMP or glucocorticoid in this study and have baseline and at least one post-treatment data for the following measures: ALT, AST, IgG, Ishak score, and autoantibodies. All observed data will be included in the data summaries.

Per Protocol (PP): A PP population may be used to analyze select efficacy endpoints and will be based on zetomipzomib exposure (time on treatment) and protocol deviations.

Safety Population: The safety population will include all randomized patients who received at least 1 dose of IMP and will be the population used for the analysis of safety data.

AE data will be coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA; Version 25.0 or later). The number and percentage of patients experiencing any treatment-emergent AE (TEAE), overall, and by system organ class and preferred term will be tabulated. Values for clinical laboratory results, vital signs, weight, and ECG findings will be tabulated for each visit.

Further details of the statistical methodology, including methods for handling missing data and early withdrawals, will be provided in a statistical analysis plan (SAP) that will be finalized prior to any planned unblinded analysis.

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments (Visits with Study Assessments) – Double-blind Treatment Period

		Double-blind Treatment														
Visit Number	**Screen[a] 1**	**2**		**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**		**20**	**22**	**24**	**26[t]**
Start of Week	**-4**	**0**		**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**		**18**	**20**	**22**	**24**
		Pre	**Post**								**Pre**	**Post**				
Study Day ± Window (Days)	**-28 to -1**	**1**		**15±1**	**29±1**	**43±1**	**57±1**	**71±1**	**85±1**	**99±1**	**113±1**		**127±1**	**141±1**	**155±1**	**169±1**
Informed consent[a]	X															
Informed consent for genotyping[b]	X															
Inclusion/exclusion criteria	X															
Demographic data	X															
Medical history (including AIH, procedures, prior therapy, social history)	X															
Concomitant therapy	X	←														→
Screening serology tests[c]	X															
TB test	X															
FSH[d]	X															
Pregnancy test[e]	X	X			X		X		X		X			X		X
Full physical examination[f]	X										X					X

		Double-blind Treatment														
Visit Number	**Screen[a] 1**	**2**		**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**		**20**	**22**	**24**	**26[t]**
Start of Week	**-4**	**0**		**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**		**18**	**20**	**22**	**24**
		Pre	**Post**								**Pre**	**Post**				
Study Day ± Window (Days)	**-28 to -1**	**1**		**15±1**	**29±1**	**43±1**	**57±1**	**71±1**	**85±1**	**99±1**	**113±1**		**127±1**	**141±1**	**155±1**	**169±1**
Abbreviated physical examination[f]		X			X		X		X					X		
Vital signs[g]	X	X		X	X	X	X	X	X	X	X		X	X	X	X
12-lead ECG[h]	X										X					X
EQ-5D-5L[i]	X										X					X
CLDQ[i]	X										X					X
GTI assessment		X														X
Hematology, IgG, autoantibodies[j], and coagulation[k]	X	X			X		X		X		X			X		X
Serum chemistry[k]	X	X		X	X	X	X	X	X	X	X		X	X	X	X
Plasma cytokines/proteomics[l]		X					X				X					X
Leukocyte subsets immunophenotyping[l]		X									X					X
Genotyping (DNA)[m]		X														
Gene expression (RNA)[m]		X					X				X					X
Blood sample for PK[n]		X	X								X	X				
Urinalysis[o]	X	X			X		X		X		X			X		X

		Double-blind Treatment													
Visit Number	**Screen[a] 1**	**2**		**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**		**20**	**22**	**24**	**26[t]**
Start of Week	**-4**	**0**		**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**		**18**	**20**	**22**	**24**
		Pre	**Post**								**Pre**	**Post**				
Study Day ± Window (Days)	**-28 to -1**	**1**		**15±1**	**29±1**	**43±1**	**57±1**	**71±1**	**85±1**	**99±1**	**113±1**		**127±1**	**141±1**	**155±1**	**169±1**
SARS-CoV-2[p]	X															
FibroScan[q]	X										X					X
Liver biopsy	X[r]															X
Randomization		X														
IMP administration[s]		X		X	X	X	X	X	X	X	X		X	X	X	
Adverse events			←													→

Abbreviations: AIH=autoimmune hepatitis; CLDQ=Chronic Liver Disease Questionnaire; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EQ-5D-5L=EuroQoL 5-dimension 5-level; FSH=follicle stimulating hormone; GTI=Glucocorticoid Toxicity Index; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; hCG=beta-human chorionic gonadotropin; HCV=hepatitis C virus; HEENT=head, eyes, ears, nose, throat; HIV=human immunodeficiency virus; IgG=immunoglobulin G; IMP=investigational medicinal product; OLE=open-label extension; PK=pharmacokinetic; Post=post-dose; Pre=pre-dose; RT-PCR=real-time polymerase chain reaction; RNA=ribonucleic acid; SARS-CoV-2=serious acute respiratory syndrome coronavirus 2; TB=tuberculosis; VCTE= vibration-controlled transient elastography

a The screening period may last up to 4 weeks; however, laboratory assessments delayed due to logistic considerations may be obtained up to an additional 7 days later, upon approval by the Sponsor. Informed consent must be signed prior to any study-related activity in KZR-616-208.

b Patients who provide additional informed consent will undergo blood sampling for genetic analysis.

c Includes HIV, HBsAg, HBcAb, HBsAb, and HCV.

d FSH testing should be done for females who are not surgically sterile (see Section 7.2.7), with amenorrhea for >1 but ≤2 years, and without documented confirmatory FSH level in the postmenopausal range.

e Women of childbearing potential only (see Section 7.2.7). Positive urine pregnancy tests will be confirmed with a serum hCG test.

f A full physical examination includes, at a minimum, assessment of the following: general appearance, skin, HEENT, heart; chest/breast, abdomen, neurological system (briefly), lymph nodes, spine, and skeletal extremities. The examination will also include body weight and height (height at Visit 2 predose only). An abbreviated physical examination, symptom -directed as determined by the Investigator, will include general appearance, cardiovascular, gastrointestinal, and pulmonary systems. The abbreviated physical examination may be performed at various unscheduled timepoints if clinically indicated.

g Vital signs (pulse rate, respiratory rate, blood pressure, and body temperature) will be collected prior to dosing. Pulse rate and blood pressure (using a calibrated sphygmomanometer) should be collected after the patient has been resting for at least 5 minutes in the seated position (pulse rate first, followed by blood pressure). If the blood pressure is elevated on the first measurement at Screening, it should be repeated after at least an additional 5 minutes of rest. It is recommended that blood pressure be measured using the same arm at each assessment. When the time of vital signs measurement coincides with a blood sample collection, the vital signs will be measured before blood sample collection.

h 12-lead ECG should be performed after the patient has been resting for at least 5 minutes in the supine position.

i It is recommended that the EQ-5D-5L and CLDQ be completed prior to any other procedures or assessments (other than signing of informed consent) at applicable visits.

j See Section 7.2.4.5 for the list of autoantibodies. In addition to the timepoints specified, samples for autoantibodies will be collected if a patient experiences a disease flare.

k Patients will be in a seated or supine position during blood collection. See Section 7.2.4.5 for assessments.

l Plasma samples for cytokines and proteomics and blood samples for immune cell profiling will be collected prior to dosing. Samples for proteomics and immune cell profiling will be stored for future analysis of chemokines and immune cell subsets.

m Samples will be collected prior to dosing in patients who have provided the proper informed consent for genetic analyses.

n Samples for PK analysis will be drawn from all patients prior to IMP administration, at 30 minutes (±10 minutes) after administration, and at 4 hours (±15 minutes) after administration. In addition, patients will be randomized 1:1:1 to 3 groups to obtain an additional PK sample at either 15 minutes (±5 minutes), 1 hour (±10 minutes), or 2 hours (±15 minutes) after IMP administration. The time of the PK blood draw must be recorded.

o A 30 mL aliquot should be obtained from the first morning void. All urinalyses will include both macroscopic and microscopic examination.

p Where local conditions and requirements mandate SARS-CoV-2 testing, these tests will be conducted prior to Visit 2. If testing is conducted, the test must be an RT-PCR assay for SARS-CoV-2, with results expected within 24 hours.

q FibroScan is a device to using VCTE to measure liver stiffness. The scan will be performed at least 2 hours after food intake.

r Results of a liver biopsy performed within 6 months prior to Screening (or at Screening) will be used as the Baseline liver biopsy. Liver biopsies will be performed and analyzed by a local laboratory.

s See Table 2 for weekly schedule of IMP administration at visits where no study assessments are performed.

t For patients who roll over immediately to the OLE Period, Study Visit 26 (Table 1) may occur on the same day as Study Visits 27 and 28 (Table 3). Patients who are not eligible or choose not to roll over to the OLE Period will have an End-of-Study (EOS) visit (see Table 3) 4 weeks after completion of the Double-blind Treatment Period.

Table 2 Schedule of Investigational Medicinal Product Administration (Visits with no Study Assessments) – Double-blind Treatment Period

	Double-blind Treatment											
Visit Number	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**
Start of Week	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**
Study Day ± Window (Days)	**8±1**	**22±1**	**36±1**	**50±1**	**64±1**	**78±1**	**92±1**	**106±1**	**120±1**	**134±1**	**148±1**	**162±1**
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: IMP=investigational medicinal product

NOTE: Home trial service will be arranged for patients who choose not to return to the site for these visits.

Table 3: Schedule of Assessments (Visits with Study Assessments) – Open-label Extension Period

	OLE Eligibility	Open-label Treatment								
Visit Number	**27[a]**	**28[a]**	**31**	**35**	**39**	**43**	**47**	**EOT**	**EOS[n]**	**ETV[o]**
Start of OLE Week		**OLE 1**	**OLE 4**	**OLE 8**	**OLE 12**	**OLE 16**	**OLE 20**	**OLE 25**	**N/A**	**N/A**
OLE Study Day ± Window (Days)	**0 (-28)**	**1**	**22±7**	**50±7**	**78±7**	**106±7**	**134±7**	**169±7**	**N/A**	**N/A**
OLE inclusion/exclusion criteria	X									
Concomitant therapy	←	—	—	—	—	—	—	→		X
Pregnancy test[b]	X		X	X	X	X	X	X	X	X
Full physical examination[c]	X					X		X		X
Abbreviated physical examination[c]			X	X	X		X		X	
Vital signs[d]	X		X	X	X	X	X	X	X	X
12-lead ECG[e]	X					X		X		X
EQ-5D-5L[f]	X					X		X		X
CLDQ[f]	X					X		X		X
GTI assessment	X							X		X
Hematology, IgG, autoantibodies[g], and coagulation[h]	X		X	X	X	X	X	X	X	X
Serum chemistry[h]	X		X	X	X	X	X	X	X	X
Urinalysis[i]	X		X	X	X	X	X	X		X
Plasma cytokines/proteomics[j]								X		X
Leukocyte subsets immunophenotyping[j]								X		X
Gene expression (RNA)[k]								X		X
FibroScan[l]	X							X		X

	OLE Eligibility	Open-label Treatment								
Visit Number	**27[a]**	**28[a]**	**31**	**35**	**39**	**43**	**47**	**EOT**	**EOS[n]**	**ETV[o]**
Start of OLE Week		**OLE 1**	**OLE 4**	**OLE 8**	**OLE 12**	**OLE 16**	**OLE 20**	**OLE 25**	**N/A**	**N/A**
OLE Study Day ± Window (Days)	**0 (-28)**	**1**	**22±7**	**50±7**	**78±7**	**106±7**	**134±7**	**169±7**	**N/A**	**N/A**
Optional liver biopsy								X		X
IMP administration[m]		X	X	X	X	X	X			
Adverse events	←								→	X

Abbreviations: AIH=autoimmune hepatitis; CLDQ=Chronic Liver Disease Questionnaire; ECG=electrocardiogram; EOS=End-of-Study; EOT=End-of-Treatment; EQ-5D-5L=EuroQoL 5-dimension 5-level; ETV=Early Termination Visit; GTI=Glucocorticoid Toxicity Index; hCG=beta-human chorionic gonadotropin; IgG=immunoglobulin G; IMP=investigational medicinal product; N/A=not applicable; OLE=open-label extension; RT-PCR=real time polymerase chain reaction; VCTE=vibration-controlled transient elastography.

[a] For patients who roll over immediately from the Double-blind Treatment Period to the OLE Period, the Week 24 Visit of the Double-blind Treatment Period (Study Visit 26) in Table 1 may occur on the same day as Study Visits 27 and 28 in Table 3. For patients who initiate the OLE Period within 4 weeks after the Week 24 Visit of the Double-blind Treatment Period, the most recently reported assessments from Week 20 or later in the Double-blind Treatment Period may serve as the eligibility assessments for the OLE Period (ie, OLE Visit 27 assessments do not need to be repeated). For patients who roll into the OLE Period >4 weeks and <12 weeks after the Week 24 Visit of the Double-blind Treatment Period, Visit 27 assessments must be performed within 28 days prior to first open-label IMP administration to confirm eligibility for the OLE. All new or changed concomitant medications and adverse events occurring after Week 24 of the Double-blind Treatment Period through Day 1 of the OLE Period should be recorded. If a patient does not meet eligibility criteria for the OLE Period, then the patient would proceed with the EOS visit. The patient would not be considered a screen fail for the OLE Period.

[b] Women of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum hCG test.

[c] A full physical examination includes, at a minimum, assessment of the following: general appearance, skin, HEENT, heart; chest/breast, abdomen, neurological system (briefly), lymph nodes, spine, and skeletal extremities. The examination will also include body weight. An abbreviated physical examination, symptom -directed as determined by the Investigator, will include general appearance, cardiovascular, gastrointestinal, and pulmonary systems. The abbreviated physical examination may be performed at various unscheduled timepoints if clinically indicated.

[d] Vital signs (pulse rate, respiratory rate, blood pressure, and body temperature) will be collected prior to dosing. Pulse rate and blood pressure (using a calibrated sphygmomanometer) should be collected after the patient has been resting for at least 5 minutes in the seated position (pulse rate first, followed by blood pressure). If the blood pressure is elevated on the first measurement at Screening, it should be repeated after at least an additional 5 minutes of rest. It is recommended that blood pressure be measured using the same arm at each assessment. When the time of vital signs measurement coincides with a blood sample collection, the vital signs will be measured before blood sample collection.

[e] 12-lead ECG should be performed after the patient has been resting for at least 5 minutes in the supine position.

[f] It is recommended that the EQ-5D-5L and CLDQ be completed prior to any other procedures or assessments at applicable visits.

[g] See Section 7.2.4.5 for the list of autoantibodies. In addition to the timepoints specified, samples for autoantibodies will be collected if a patient experiences a disease flare.

[h] Patients will be in a seated or supine position during blood collection. See Section 7.2.4.5 for assessments.

[i] A 30 mL aliquot should be obtained from the first morning void. All urinalyses will include both macroscopic and microscopic examination.

[j] Plasma samples for cytokines and proteomics and blood samples for immune cell profiling will be collected prior to dosing. Samples for proteomics and immune cell profiling will be stored for future analysis of chemokines and immune cell subsets.

[k] Samples will be collected prior to dosing in patients who have provided the proper informed consent for genetic analyses.

[l] FibroScan is a device to using VCTE to measure liver stiffness. The scan will be performed at least 2 hours after food intake.

[m] See Table 4 for weekly schedule of IMP administration at visits where no study assessments are performed.

[n] The EOS (safety follow-up) visit has a ±7 day visit window.

[o] If a patient cannot continue with the planned assessments, the patient will complete the ETV followed by the End-of-Study (EOS) visit 4 weeks later.

Table 4: Schedule of Investigational Medicinal Product Administration (Visits with no Study Assessments) – Open-label Extension Period

	Open-label Treatment																	
Visit Number	**29**	**30**	**32**	**33**	**34**	**36**	**37**	**38**	**40**	**41**	**42**	**44**	**45**	**46**	**48**	**49**	**50**	**51**
Start of Week	**OLE 2**	**OLE 3**	**OLE 5**	**OLE 6**	**OLE 7**	**OLE 9**	**OLE 10**	**OLE 11**	**OLE 13**	**OLE 14**	**OLE 15**	**OLE 17**	**OLE 18**	**OLE 19**	**OLE 21**	**OLE 22**	**OLE 23**	**OLE 24**
Study Day ± Window (Days)	**8±3**	**15±3**	**29±3**	**36±3**	**43±3**	**57±3**	**64±3**	**71±3**	**85±3**	**92±3**	**99±3**	**113±3**	**120±3**	**127±3**	**141±3**	**148±3**	**155±3**	**162±3**
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: IMP=investigational medicinal product.

NOTE: Home trial service will be arranged for patients who choose not to return to the site for these visits.

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
6-MP	6-Mercaptopurine
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immune deficiency syndrome
AIH	Autoimmune hepatitis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AZA	Azathioprine
BUN	Blood urea nitrogen
CAP	Controlled attenuation parameter
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CI	Confidence interval
CLDQ	Chronic Liver Disease Questionnaire
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CR	Complete remission
CsA	Cyclosporine A
DILI	Drug-induced liver injury
DM	Dermatomyositis
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End-of-Study
EOT	End-of-Treatment
EQ-5D-5L	EuroQol 5-dimension 5-level
EQ-VAS	EuroQol visual analog scale
ETV	Early Termination Visit
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviation or Term	Definition
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GTI	Glucocorticoid Toxicity Index
GTI-AIS	GTI Aggregate Improvement Score
GTI-CWS	GTI Cumulative Worsening Score
HAI	Histological Activity Index
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
hCG	Beta-human chorionic gonadotropin
HCV	Hepatitis C virus
HEENT	Head, eyes, ears, nose, throat
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IGRA	Interferon-gamma release assay
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
IV	Intravenous
LDA	Longitudinal data analysis
LMP	Low molecular mass polypeptide
LN	Lupus nephritis
LSM	Liver stiffness measurement
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MLL	Mixed lineage leukemia
MMF	Mycophenolate mofetil
MMRM	Mixed model for repeated measures
MMS	Mycophenolate sodium
MPA	Mycophenolic acid
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation or Term	Definition
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic
PM	Polymyositis
PR	Partial remission
QTcF	QC interval corrected for pulse rate by Fridericia's formula
QW	Once weekly
RNA	Ribonucleic acid
RT-PCR	Real-time polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SD	Standard deviation
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SUSAR	Suspected unexpected serious adverse reaction
TAC	Tacrolimus
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
T_{max}	Time of maximum plasma concentration
ULN	Upper limit of normal
US	United States
VCTE	Vibration-controlled transient elastography
WFI	Water for injection
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. INTRODUCTION

Study KZR-616-208 is a randomized, double-blind, placebo-controlled, Phase 2a study with an open-label extension (OLE) to evaluate the safety, tolerability, and efficacy of zetomipzomib (KZR-616) in patients with autoimmune hepatitis (AIH) who have failed standard-of-care treatment, had an incomplete biochemical response to ≥3 months of standard-of-care treatment, or had a disease flare after experiencing complete remission induced by standard-of-care treatment. The definition of biochemical response is per the current 2020 American Association for the Study of Liver Diseases (AASLD) practice guidance for the diagnosis and management of AIH in Adults and Children (Mack et al., 2020).

1.1. Zetomipzomib Background

Zetomipzomib is a first-in-class tripeptide ketoepoxide-based selective inhibitor of the human immunoproteasome. Inhibition of the immunoproteasome results in an immunomodulatory response characterized by reduction in pro-inflammatory cytokine release, inhibition of inflammatory T-cell subsets and a reduction in autoantibody levels and plasma cells in preclinical models of autoimmune disease (Muchamuel et al., 2009; Ichikawa et al., 2012; Kalim et al., 2012). Based on broad immunomodulatory activity across both the innate and acquired immune system, zetomipzomib represents a potential novel therapeutic for multiple disorders of the immune system regardless of disease etiology.

Preclinical studies show that zetomipzomib results in potent and selective inhibition of the immunoproteasome in human cells in vitro, in blood and tissues when administered to rodents, and in blood when administered to monkeys. Near complete recovery of immunoproteasome activity in immune cell rich tissues such as the spleen occurred within 7 days of dosing. Inhibition of immunoproteasome active site subunits by zetomipzomib, specifically the low molecular mass polypeptide (LMP) subunits LMP7, LMP2, and the multicatalytic endopeptidase complex-like (MECL) subunit MECL1, occurs through an irreversible mechanism, similar to that for carfilzomib, a Food and Drug Administration (FDA)-approved agent and analog of zetomipzomib (Bennett and Kirk, 2008; Huber et al., 2012; KYPROLIS®, 2012). Peptide ketoepoxides show no off-target activity (Arastu-Kapur et al., 2011; Kisselev et al., 2012). Zetomipzomib forms a dual covalent adduct with the N-terminal Thr residue of proteasome active sites. There are 8 known N-terminal threonine proteases in the genome, 7 proteasome active sites (β1, β2, β5, LMP2, LMP7, MECL1, and β5t) and Taspase 1, an endopeptidase involved in activity of the mixed lineage leukemia (MLL) gene product. Thus, the anti-inflammatory and immunomodulating effects of zetomipzomib is achieved only through action on the immunoproteasome.

To date, 2 studies in healthy volunteers using doses ranging from 7.5 to 75 mg zetomipzomib weekly have been completed. In addition, a Phase 1b/2 study in patients with lupus nephritis (LN) (KZR-616-002) and a Phase 2 study in patients with dermatomyositis (DM) or polymyositis (PM) (KZR-616-003) have recently completed. An OLE study in patients with DM or PM, KZR-616-003E, is ongoing. Data from the KZR-616-002 study demonstrated improvement in multiple exploratory efficacy measures of disease activity across organ systems (including the Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K]), proteinuria, and autoantibodies after 24 weeks of treatment, without evidence of significant immunosuppression. Topline results of the KZR-616-003 study showed that most patients with

DM or PM saw clinically meaningful improvements in the components of the Total Improvement Score (TIS), although zetomipzomib demonstrated no significant differentiation from placebo control. Results from zetomipzomib studies to date are discussed in more detail in Section 1.4.

1.2. Rationale for Use of Zetomipzomib in the Proposed Study Populations, and Rationale for the Study

AIH is a rare, severe, autoimmune disease that without treatment results in fulminant hepatic failure. AIH is the initial stage of serial subsequent liver diseases including cirrhosis and hepatocellular carcinoma (Kirstein et al., 2015). The prevalence of AIH ranges from 16 to 18 cases per 100,000 persons in Europe (Lowe and John, 2018). In the United States (US), AIH prevalence is as high as 31.2/100,000, affecting less than 200,000 individuals in the US (Beretta-Piccoli et al., 2021; Tunio et al., 2021). In Europe and in the US, AIH accounts for 2% to 3% of the pediatric and 4% to 6% of the adult liver transplantations (Lowe and John, 2018).

Current first-line therapy for AIH is chronic administration of high-dose glucocorticoids (Mack et al., 2020). The usual treatment paradigms include higher-dose induction therapy followed by dose tapering to the lowest tolerated dose that also controls inflammation of the liver and is titrated to liver transaminases, specifically alanine aminotransferase (ALT). Patients with AIH require anti-inflammatory therapy for life. Second-line induction and maintenance therapies include glucocorticoid-sparing treatments such as azathioprine (AZA), mycophenolate mofetil (MMF), calcineurin inhibitors, and B-cell depleting therapies (eg, rituximab).

AIH can respond favorably to standard-of-care, and though most patients accrue some degree of hepatic fibrosis, only 10-15% progress to end-stage liver disease with current treatments. However, the adverse effects of high-dose glucocorticoid therapies create an additional burden for patients resulting in diabetes mellitus, osteoporosis, muscle atrophy, centripetal weight gain, Cushing facies, and diminished defense against multiple infections (Poetker and Reh, 2010). Thus, there is a high unmet need for glucocorticoid-sparing therapies.

AIH disease pathophysiology is not well understood, and predictive animal models are lacking (Sebode et al., 2018), but contributions of dysregulated B- and T- cells as well as monocytic cells likely underlie disease etiology. The immunopathogenesis of AIH comprises (1) autoreactive CD4 and CD8 T cells that break self-tolerance to hepatic autoantigens, (2) autoantibodies produced by autoreactive B cells in the absence of effective B regulatory cell inhibition (Mack et al., 2020), (3) selective immunoglobulin G (IgG) elevation that supports B cell involvement in AIH (Sebode et al., 2018), and (4) elevated expression levels of Vav guanine nucleotide exchange factor 1 (VAV1) and p21-activated kinase 1 (PAK1) in liver monocytes/Kupffer cells which are associated with disease progression (Lin et al., 2016). These effector cells, also implicated in the pathogenesis of AIH, have been shown to be targeted by immunoproteasome inhibition (Kirk et al., 2021).

As zetomipzomib is a selective inhibitor of the human immunoproteasome without off-target activities, it may achieve immunomodulation by specifically targeting the immunoproteasome, and result in similar therapeutic potential to glucocorticoids without any off-target effects or frank immunosuppression, thus providing a glucocorticoid-sparing/glucocorticoid-free therapy for AIH.

Study KZR-616-208 will provide proof-of-concept for both remission induction and remission maintenance of AIH with zetomipzomib.

1.3. Rationale for Study Endpoints

The unmet medical needs for AIH are glucocorticoid-sparing/glucocorticoid-free remission induction and remission maintenance. Glucocorticoid dose reduction, glucocorticoid-related side effects, reduction of liver stiffness, and health-related quality of life assessment have been widely used as outcome measures for clinical trials in AIH (Schramm, 2019). According to a recent publication regarding effective trial design for AIH, 24 weeks of active treatment is a sufficient length of time to achieve remission induction (Schramm, 2019). However, the optimal timepoints for zetomipzomib to achieve remission in AIH patients have not been identified. Complete biochemical remission (ALT, aspartate aminotransferase [AST], immunoglobulin G [if IgG levels are high at Baseline]) is the best surrogate marker for histological remission, and thus for a favorable disease course. Therefore, the primary efficacy endpoint for the Double-blind Treatment Period of this study is the proportion of patients who achieve normalization of ALT, AST, and IgG (complete remission [CR]) by Week 24 or earlier with glucocorticoid dose not higher than the starting dose (at Baseline). The primary efficacy endpoint will be analyzed at Weeks 12, 16, 20 and 24 to help determine an optimal timepoint for achieving remission in AIH patients with zetomipzomib treatment. The key secondary efficacy endpoints are the changes from Baseline in ALT level at Weeks 12, 16, 20 and 24, the proportion of patients who achieve partial remission (PR), time to CR, and the proportion of patients not responding to treatment (ie, treatment failures).

The OLE Period of the study will allow monitoring of safety and efficacy beyond 24 weeks in patients who were randomized to zetomipzomib during the Double-blind Treatment Period. Patients who were randomized to placebo in the Double-blind Treatment Period will be treated with zetomipzomib for the first time during the OLE Period, and the safety/efficacy will be compared with the patient's experience on 24 weeks of placebo. Key additional efficacy endpoints are the proportion of patients experiencing a disease flare among the patients who achieved a CR and the patients who have a CR or PR among the patients who did not achieve a CR or PR during the Double-blind Treatment Period. The mean changes in prednisone/prednisone equivalent dose will also be assessed for zetomipzomib as potential glucocorticoid-sparing/glucocorticoid-free medication for the treatment of AIH.

1.4. Summary of Potential Risks and Benefits

Despite advances in understanding and treatment of AIH, important unmet clinical needs remain in both adult and pediatric patient populations (Jones et al., 2018). The current study is to assess the safety and efficacy of the first-in-class targeted selective molecule for patients with AIH which is designed to reduce organ (liver) inflammation and damage, be safe to be used as maintenance therapy, and that could reduce or obviate the need for immunosuppressive therapies, including glucocorticoids.

Zetomipzomib is a selective and irreversible inhibitor of the immunoproteasome, which controls key intracellular processes in immune effector cells. The nonclinical pharmacologic, pharmacokinetic (PK), and toxicologic properties of zetomipzomib have been thoroughly evaluated. This nonclinical data supports investigation of zetomipzomib as a selective and

irreversible inhibitor of the immunoproteasome, which controls key intracellular processes in immune effector cells in patients with autoimmune diseases, including but not limited to models of rheumatoid arthritis, the progression of nephritis in 2 mouse models of systemic lupus erythematosus (SLE), and in the C-protein induced myositis mouse model of myositis. It should be noted that no relevant nonclinical model of AIH exists at this time. Zetomipzomib could provide a meaningful potent anti-inflammatory treatment potentially without immunosuppression or significant off-target effects found with currently available therapies.

Zetomipzomib showed preliminary evidence of clinical activity in adult patients with SLE and LN (KZR-616-002) through improvement in proteinuria, reduction in autoantibodies (anti-ds-DNA antibodies), and improvements in extra-renal disease activity.

Nonclinical toxicity studies of zetomipzomib include single- and repeat-dose studies in rats and monkeys, immunotoxicity, safety pharmacology, embryofetal development, fertility, local irritation study in pigs, and genotoxicity studies. Of note, especially for patients with autoimmune disease who are often of childbearing potential, no teratogenicity was demonstrated. Repeat-dose toxicity studies of zetomipzomib in rats and monkeys involved once weekly subcutaneous (SC) administration for 6- and 9-months duration, respectively. No signs of hepatotoxicity or immunotoxicity were noted in these studies.

Across separate studies in healthy volunteers to evaluate safety, tolerability, PK and pharmacodynamics (PD) (KZR-616-001 and KZR-616-004), zetomipzomib was administered to 100 subjects as single and weekly intravenous (IV) or SC doses ranging from 7.5 to 75 mg. Exposure to zetomipzomib is dose proportional across this range of doses and total exposure at 75 mg is roughly equivalent to that seen in 6-month repeat dose toxicity study in rats. Zetomipzomib is cleared rapidly following single SC administration with a mean terminal half--life of ~5 hr and extrahepatic clearance based on IV administration. No accumulation of zetomipzomib was noted with repeated weekly SC administration. Metabolism occurs via microsomal epoxide hydrolase, a ubiquitously expressed enzyme which is non-saturable. The predominant metabolite found in human plasma is the inactive diol. At doses ≥30 mg, zetomipzomib induces selective inhibition of immunoproteasome enzymatic activity exceeding 80% with recovery occurring between weekly doses and no impact of repeat dosing on PD. At doses of 45 and 60 mg, the level of inhibition is at or near the lower limit of quantitation, while inhibition of the constitutive protease is <40%, demonstrating selectivity for the immunoproteasome in humans.

Patients will be closely monitored for safety. For adult patients with autoimmune diseases who were treated with zetomipzomib, systemic injection reaction is an important potential risk. Systemic injection reaction has presented as hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills. In addition, the most common adverse events (AEs) at any dose were predominantly injection site reactions such as erythema, induration, and tenderness (pain), which were generally mild and transient in nature and did not appear to increase in severity or frequency with repeated dosing of zetomipzomib. Injection site reaction is an identified risk for zetomipzomib. Patients will be monitored for the aforementioned signs and symptoms.

The effects of zetomipzomib on embryogenesis, reproduction, and spermatogenesis in humans are unknown. No formal studies have been conducted with zetomipzomib in pregnant women or during breastfeeding. In nonclinical studies, zetomipzomib tested positive for mammalian

chromosomal aberration, but did not have clastogenic activity in animal studies and was not found to have direct teratogenic effects in rats and rabbits. In addition, zetomipzomib had no toxicological effect on mating or fertility in male and female rats. Study patients should be advised to use effective contraception during and after zetomipzomib treatment as described in respective protocols.

The potential risks identified in association with zetomipzomib are justified by the anticipated benefits that may be afforded to patients with AIH. Given the modulatory action on immune effector cells without suppressive effects on cell generation, zetomipzomib is well positioned to be a meaningful anti-inflammatory agent and potentially glucocorticoid-sparing treatment option for patients with AIH.

For additional information, please refer to the current version of the zetomipzomib (KZR-616) Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

The safety objective is to evaluate the safety and tolerability of zetomipzomib in patients with AIH.

The efficacy objective for the Double-blind Treatment Period is to evaluate the efficacy of zetomipzomib in addition to standard-of-care in patients with AIH who have failed standard-of-care treatment, had an incomplete biochemical response to ≥3 months of standard-of-care treatment, or had a disease flare after experiencing complete remission induced by standard-of-care treatment. The efficacy objective for the OLE Period is to evaluate the long-term efficacy of zetomipzomib in patients with AIH.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The primary safety endpoint for both the Double-blind Treatment Period and the OLE Period is the proportion of patients who experience AEs and serious adverse events (SAEs). Other safety endpoints include:

- Incidence, nature, and severity of AEs and SAEs
- Incidence of AEs leading to investigational medicinal product (IMP) discontinuation and dose reduction
- Changes in standard laboratory parameters, vital signs, and ECGs

2.2.2. Definitions Related to Efficacy Endpoints

The Baseline ALT, AST, and IgG values will be calculated as the mean of all collected Screening and Day 1 values. Relative reduction in ALT, AST, and IgG (if IgG level is elevated at Baseline) will be calculated as the percentage change from the Baseline value.

Successful glucocorticoid taper: Prednisone/prednisone equivalent dose tapered from the starting dose (at Baseline) to a prednisone/prednisone equivalent dose of ≤10 mg/day by Week 24 or earlier.

Complete biochemical remission (CR): Normal ALT, AST, and IgG values (if IgG level is elevated at Baseline) with glucocorticoid dose not higher than starting dose (at Baseline).

Partial biochemical remission (PR): ALT, AST, and IgG values (if IgG level is elevated at Baseline) with glucocorticoid dose not higher than starting dose (at Baseline) meeting one of the following criteria:

- > upper limit of normal (ULN) but <2 × ULN (values must be lower than Baseline)
- >ULN with >80% improvement from Baseline.

Responder: Patients who achieve a reduction from Baseline in ALT, AST, and IgG (if IgG level is elevated at baseline) of ≥25% with glucocorticoid dose not higher than starting dose (at Baseline).

Sustained responder: Responders in the Double-blind Treatment Period who have sustained or further improved ALT, AST and IgG (if IgG level is elevated at Baseline) levels throughout the OLE Period with glucocorticoid dose not higher than starting dose (at Baseline).

Non-responder: Patients who do not achieve a reduction from Baseline in ALT or AST of ≥25%. Patients who have insufficient data for response determination at a time point will be considered non-responders for that time point.

Treatment failure:

- Patient's ALT or AST level worsened ≥2 times that of the Baseline value that is sustained for ≥1 week as verified via repeat laboratory assessments, despite compliance with standard of care (ie, with regard to inclusion criteria) or protocol-defined therapy.
- If a glucocorticoid dose is increased above the Baseline dose, it may be considered a treatment failure unless attributed to an adverse event not relating to AIH.

Disease flare: Elevation of ALT after achieving CR that meets all the following criteria:

- is ≥25% above the CR value
- is ≥1.25 ULN
- is sustained for ≥1 week as verified via repeat laboratory assessments
- requires the patient to re-start or escalate glucocorticoid therapy
- is not due to other identifiable causes (eg, viral hepatitis, concomitant medications, alcoholic liver injury, etc.)

2.2.3. Efficacy Endpoints

2.2.3.1. Double-blind Treatment Period

2.2.3.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who achieve CR by Week 24; analyses will also be performed on data collected at Weeks 12, 16, and 20.

2.2.3.1.2. Secondary Efficacy Endpoints

- Change from Baseline in ALT at Weeks 12, 16, 20, and 24
- Proportion of patients who achieve PR at Week 12, 16, 20, and 24
- Time to CR
- Time to PR
- Proportion of patients experiencing a disease flare after CR
- Proportion of patients who are treatment failures
- Proportion of patients who achieve CR or PR with successful glucocorticoid taper by Week 24; analyses will also be performed on data collected at Weeks 12, 16, and 20.

2.2.3.1.3. Exploratory Efficacy Endpoints

- Proportion of patients who achieve ALT normalization based on Prati criteria (males, 30 U/L; females, 19 U/L) (Prati et al., 2002), with successful glucocorticoid taper, by Week 24
- Mean changes from Baseline in AST at Weeks 12, 16, 20, and 24
- Mean changes from Baseline in IgG at Weeks 12, 16, 20, and 24
- Mean changes from Baseline in glucocorticoid dose
- Change from Baseline in the Glucocorticoid Toxicity Index (GTI) Cumulative Worsening Score (GTI-CWS) and the Aggregate Improvement Score (GTI-AIS)
- Mean changes from Baseline in inflammatory cytokines at Weeks 8, 16, and 24
- Change from Baseline in liver stiffness at Week 24, assessed by vibration-controlled transient elastography (VCTE) utilizing Fibroscan®
- Mean change from Baseline in the EuroQol 5-dimension 5-level (EQ-5D-5L) at Weeks 16 and 24
- Mean change from Baseline in the Chronic Liver Disease Questionnaire (CLDQ) at Weeks 16 and 24
- Change from Baseline in liver histopathology at Week 24, based on Ishak score (modified Histological Activity Index [HAI]) scores (Ishak et al., 1995)

2.2.3.2. Open-label Extension Period

2.2.3.2.1. Primary Efficacy Endpoints

- Proportion of patients experiencing a disease flare among the patients who achieved a CR during the Double-blind Treatment Period

2.2.3.2.2. Exploratory Efficacy Endpoints

- Proportion of patients who have a CR or PR among the patients who did not achieve a CR or PR during the Double-blind Treatment Period
- Proportion of patients who have a CR or PR with successful glucocorticoid taper who did not achieve a CR or PR during Double-blind Treatment Period
- Proportion of patients who achieve a glucocorticoid-free CR
- Proportion of patients who achieve a glucocorticoid-free PR
- Mean changes in ALT
- Mean changes in AST
- Mean changes in IgG
- Mean change in the EQ-5D-5L
- Mean change in CLDQ

- Change in the GTI-CWS and the GTI-AIS
- Mean change in liver stiffness, assessed by VCTE utilizing Fibroscan®
- Change in liver histopathology, based on Ishak score (modified HAI) scores (Ishak et al., 1995)

2.2.4. Pharmacokinetic Endpoints

- Zetomipzomib and its metabolite KZR-59587 PK (maximum concentration [C_{max}], time of maximum concentration [T_{max}], area under the concentration-time curve [AUC])

3. STUDY DESIGN

3.1. Type and Design of Study

This is a Phase 2a, multi-center, randomized, double-blind, placebo-controlled study with an OLE Period to evaluate the safety, tolerability, and efficacy of zetomipzomib in patients with AIH who have failed standard-of-care treatment, had an incomplete biochemical response to ≥3 months of standard-of-care treatment, or had a disease flare (relapse) after experiencing complete remission induced by standard-of-care treatment. Incomplete biochemical response is defined as an improvement of laboratory and histological findings that are insufficient to satisfy criteria for remission (Mack et al., 2020). Disease flare or relapse is defined as an exacerbation of disease activity after induction of remission and drug withdrawal (or nonadherence) (Mack et al., 2020).

Independent Data Monitoring Committee (IDMC) will review safety findings as described in Section 9.11.

3.1.1. Double-blind Treatment Period

In the Double-blind Treatment Period, zetomipzomib or placebo will be administered weekly for a 24-week treatment period. Patients will be evaluated for eligibility according to the entry criteria (see Section 4) within 4 weeks prior to the first dose of IMP on Day 1 (Visit 2). Efficacy assessments will be performed for all patients at Weeks 12, 16, 20, and 24; these assessments are discussed in Section 7.2.2. Safety will be assessed throughout the study by monitoring of vital signs, clinical laboratory tests, and physical examinations, and by recording and analyzing all AEs and SAEs.

Eligible patients will be randomized in a 2:1 ratio on Day 1 (Visit 2) to receive either standard-of-care (glucocorticoids) with zetomipzomib (Active Treatment group), or standard-of-care with Placebo (Control group). Zetomipzomib and placebo (ie, sterile water for injection [WFI] in an equivalent volume to the reconstituted zetomipzomib dose) will be administered SC once weekly by study personnel at the site or by a home trial service at the patient's home or alternate location (eg, place of employment). The first dose of IMP will be 30 mg zetomipzomib or placebo, followed by weekly doses of 60 mg zetomipzomib or placebo for the remaining 23 weeks of the Double-blind Treatment Period.

Enrolled patients will be on standard-of-care with a prednisone/prednisone equivalent dose of 20 mg/day on Day 1 (Visit 2). Following consultation with the Medical Monitor, patients who are taking a prednisone/prednisone equivalent dose higher than 20 mg/day at Baseline may also be enrolled in the study provided the prednisone/prednisone equivalent dose does not exceed 40 mg/day. Patients are encouraged to undergo a glucocorticoid taper of prednisone/prednisone equivalent dose according to the protocol-suggested glucocorticoid taper schedule (Table 6) and prednisone equivalent doses (Table 7) as provided in Appendix B. Patients taking budesonide who are unwilling to switch to a prednisone/prednisone equivalent for the study may continue to take budesonide at the doses shown in Appendix B.

In addition to prednisone/prednisone equivalent, patients may continue to use up to two additional immunosuppressive agents if these agents are already used as baseline therapy:

a) Oral AZA *or* oral MMF (including the alternatives mycophenolate sodium [MMS] or mycophenolic acid [MPA])
and/or

b) Oral tacrolimus (TAC), cyclosporine A (CsA), or 6-mercaptopurine (6-MP)

The dose of these immunosuppressants must be stable for at least 4 weeks prior to Screening and must be held constant unless tolerability/AEs require dose adjustment and glucocorticoid taper is completed. Following completion of the glucocorticoid taper, immunosuppressants may be decreased at the Investigator's discretion (Section 6.2.3).

During the glucocorticoid taper, patients with signs and symptoms of worsening disease (ie, worsening of ALT level ≥25% from Baseline for ≥1 week, as verified via repeat laboratory assessments) may increase glucocorticoid doses following consultation with the Medical Monitor.

For patients who are confirmed treatment failures or who experience a disease flare (see Section 2.2.2) during the treatment period, IMP may be discontinued upon consultation with the Medical Monitor, and additional care will be introduced as medically indicated. Patients who receive rescue therapy (see Section 6.3) will temporarily discontinue IMP, complete the Double-blind Period visits, and remain eligible for the OLE Period. Patients who do not receive rescue therapy but undergo a temporary interruption in IMP (≤2 consecutive doses or ≤4 total doses) should also remain in the study. Patients who discontinue participation in the study due to a disease flare will be considered treatment failures. If the patient cannot continue with the planned assessments, the patient will complete the Early Termination Visit (ETV; Table 3) followed by the End-of-Study (EOS) visit (Table 3) 4 weeks later.

A liver biopsy will be performed at the Week 24 visit to assess any changes from Baseline in liver histopathology.

Patients who are eligible to roll over to the OLE Period will receive their first SC injection of zetomipzomib at the dose and schedule described in the OLE Period section (Section 3.1.2). Patients who are not eligible or choose not to roll over to the OLE Period will have an End-of-Study (EOS) visit (assessments shown in Table 3) 4 weeks after completion of the Double-blind Treatment Period.

3.1.2. Open-label Extension (OLE) Period

Patients who complete the Double-blind Period study visits through Week 24 are eligible to roll over to the OLE Period. If a patient does not meet eligibility criteria for the OLE Period, then the patient would proceed with the EOS visit. The patient would not be considered a screen fail for the OLE Period.

All patients will receive a SC injection of 30 mg zetomipzomib at the OLE Week 1 visit, followed by weekly SC injections of 60 mg zetomipzomib, administered by study personnel at the site or by a home trial service at the patient's home or alternate location (eg, place of employment), for a total of 24 additional weeks of treatment. After the OLE Week 1 Visit, additional on-site study visits will occur every 4 weeks from OLE Week 4 through OLE

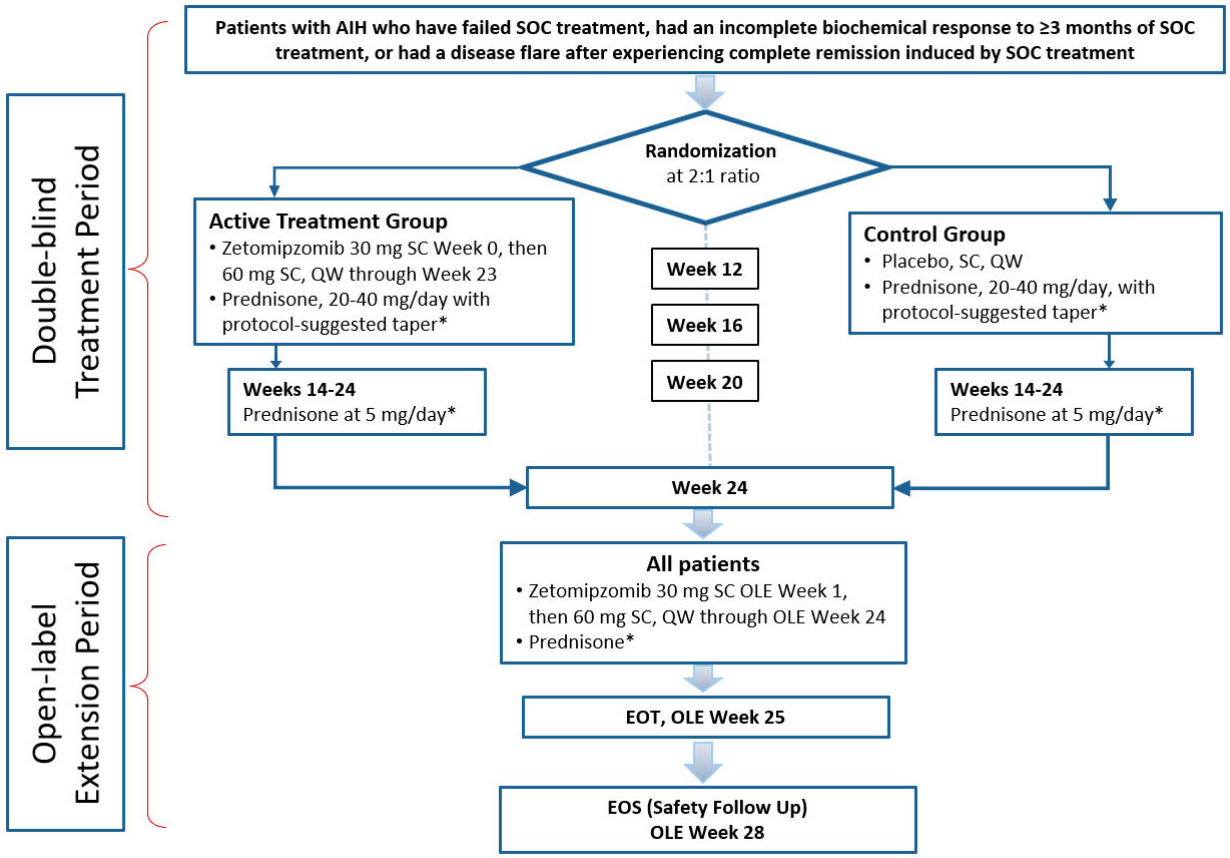
Week 20. An additional on-site visit will occur at OLE Week 25 (EOT visit). At these visits, safety and efficacy assessments will be performed according to the OLE Schedule of Assessments (Table 3). Patients will have a safety follow-up visit (EOS Visit) 4 weeks after their last dose of zetomipzomib, for a maximum potential length of participation in the OLE of 28 weeks.

During the course of the OLE Period, prednisone/prednisone equivalent can continue to be tapered and may be withdrawn (see Appendix B for suggested taper schedule). Patients with signs and symptoms of worsening disease (ie, worsening of ALT level ≥25% from OLE Baseline for ≥1 week, as verified via repeat laboratory assessments) may increase glucocorticoid doses following consultation with the Medical Monitor. For patients who are confirmed treatment failures or who experience a disease flare (see Section 2.2.2) during the OLE Period, IMP may be discontinued upon consultation with the Medical Monitor, and additional care will be introduced as medically indicated. Patients who receive rescue therapy (see Section 6.3) will temporarily discontinue IMP but will remain in the study to complete OLE visits. Patients who do not receive rescue therapy but undergo a temporary interruption in IMP (≤2 consecutive doses or ≤4 total doses) should also remain in the study. Patients who discontinue participation in the study due to a disease flare will be considered treatment failures. If the patient cannot continue with the planned assessments, the patient will complete the ETV (Table 3) followed by the End-of-Study (EOS) visit (Table 3) 4 weeks later.

An optional liver biopsy may be performed at the OLE Week 25 visit to assess changes in liver histopathology.

3.1.3. Study Design Schema

Figure 1 Study KZR-616-208 Study Design Schema



Abbreviations: AIH=autoimmune hepatitis; EOS=End-of-Study; EOT=End-of-Treatment; QW=once weekly; OLE=open-label extension; SC=subcutaneous; SoC=standard-of-care

Note: Patients who are not eligible or choose not to roll over to the OLE Period will have an EOS visit (safety follow up) 4 weeks after completion of the Double-blind Treatment Period. * For protocol-suggested glucocorticoid taper schedule, refer to Table 6 and Table 7 for prednisone equivalents in Appendix B.

3.1.4. Study Design Rationale

This is a Phase 2a, multi-center, randomized, double-blind, placebo-controlled study with an OLE Period to evaluate the safety and efficacy of zetomipzomib in patients with AIH. The study will consist of a 24-week Double-blind Treatment Period, a 24-week OLE Period, and a 4-week off-treatment safety follow-up period.

Zetomipzomib is a first-in-class selective inhibitor of the human immunoproteasome that may offer distinct advantages to the treatment and care of patients with AIH. The pathophysiology of AIH is attributed to autoimmune based dysfunction that involves T-cells, B-cells, and monocyte/macrophages including resident Kupffer cells. The foundation of current care is high-dose glucocorticoids given chronically over years or given with glucocorticoid-sparing therapies. The current standard of care is immunosuppressive agents, which are associated with significant comorbidities and toxicities. Zetomipzomib given once weekly results in an immunomodulatory effect that does not deplete cell lines or interfere with important immune-signaling targets. Zetomipzomib activity is highly specific, targeting N-terminal threonine proteases, which are only found within the immunoproteasome; thus, no off-target activities are predicted or have been seen in clinical trials to date.

Zetomipzomib is metabolized by extrahepatic epoxide hydrolase enzymes, so its metabolism would likely not be impacted by patients with liver dysfunction. The current study design enables evaluation of the safety and efficacy of zetomipzomib in patients with AIH. This study will also begin to describe potential glucocorticoid-sparing attributes, as a protocol-suggested glucocorticoid taper is included. This study should provide sufficient evidence of the safety and efficacy of zetomipzomib to inform a later phase trial of zetomipzomib for the treatment and prevention of disease flares in AIH.

3.2. Randomization, Blinding, and Unblinding Procedures

3.2.1. Randomization

This is a Phase 2a, multi-center, randomized, double-blind, placebo-controlled study with an OLE Period. Once patients have consented, undergone all screening procedures, and been determined to be eligible for the study, they will return for the Baseline (Day 1) Visit to be randomized in a 2:1 ratio to receive weekly SC administration of zetomipzomib plus standard-of-care or placebo control plus standard-of-care during the Double-blind Treatment Period.

Patients will be stratified by glucocorticoid use at Screening (ie, glucocorticoid use, no glucocorticoid use at Screening).

Additional details on randomization procedures will be provided in the Interactive Response Technology (IRT) Manual.

3.2.2. Blinding

To preserve the double-blind design, patients randomized to the placebo group will receive a SC injection in an equivalent volume to the active treatment IMP. The dosing schedule in the placebo group will be the same as that of the active treatment IMP. Thus, the double-blind nature of this study preserves the blind with respect to active study treatment and placebo.

All study personnel and study patients will be blinded to the IMP administered during the Double-blind Treatment Period. Zetomipzomib and placebo will be identical in volume (see Section 5.1). An unblinded Pharmacist will prepare and blind the IMP (see Section 6.1). The randomization code key will not be available to the Study Monitors, project statisticians, or the project team at Kezar or its representatives. The site personnel, Monitors, and study patients will remain blinded to Double-blind Treatment Period IMP assignment until the end of the study. In case of emergency, the unblinding process in Section 3.2.3 should be followed. Measures will be in place at the Sponsor to prevent unblinding by laboratory measurements.

3.2.3. Unblinding

In the rare event that a treatment-emergent adverse event (TEAE) or pregnancy occurs for which knowledge of the IMP administered is necessary to manage the patient's condition, the code for that patient may be broken and the test substance identified via the IRT system. Procedures for unblinding will be provided in the IRT Manual.

If emergency unblinding is required, the Investigator should contact the Medical Monitor prior to unblinding whenever possible. However, the Investigator is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel prior to unblinding. The reason for unblinding must be documented and captured directly within the IRT system. The IRT system will automatically store the date and time of unblinding.

Individual patient data will be unblinded for pharmacovigilance regulatory reporting purposes. Patients whose data have been unblinded for pharmacovigilance regulatory reporting purposes only will not be discontinued from further receipt of IMP.

In the case of accidental unblinding, immediate measures must be taken to contain the unblinding. The accidental unblinding should be promptly documented and reported to the Sponsor, who will advise on further actions.

3.3. Number of Sites

Up to 24 sites are planned to participate in this study.

4. PATIENT SELECTION AND ENROLLMENT

4.1. Number of Patients

Approximately 24 patients (randomized in a 2:1 ratio; Active Treatment group: Control group) will be enrolled in the study.

Patients will be evaluated for eligibility in the study according to the eligibility criteria. The Investigator will ensure that the patient has provided written informed consent before administration of study medication.

Once informed consent is obtained, the evaluations may begin to assess study eligibility (inclusion/exclusion criteria). Patients who do not meet inclusion/exclusion criteria may be rescreened one time.

4.2. Inclusion Criteria

Only individuals who meet all of the following criteria may be enrolled in the study.

Double-blind Treatment Period

1. Must be aged ≥18 years.
2. Must have a clinical diagnosis of AIH and signs of active disease despite standard-of-care therapy for ≥3 months or disease flare after experiencing complete remission induced by standard-of-care treatment, including:
   a. Screening ALT values that are 1.25 to 10 times ULN
   b. Liver biopsy results with Ishak score (modified HAI) ≥5/18 (Ishak et al., 1995) indicating active AIH, from a biopsy performed at Screening or within 6 months prior to Screening.
   c. Mild or no hepatic impairment (Child-Pugh category A)
3. Must be willing to use and taper glucocorticoid therapy as described in Section 3.1 and Section 6.2.2.1.
4. Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test prior to the first dose of IMP in KZR-616-208, and must agree to continue to use a highly effective method of birth control until completion of the study (or 30 days following the last dose of IMP in case of early withdrawal). For the purposes of this study, WOCBP are defined as fertile female patients, unless the patient is postmenopausal (defined by amenorrhea for at least 2 years or amenorrhea for at least 1 year with confirmatory follicle stimulating hormone [FSH] level in the postmenopausal range, as documented historically or measured by the central or local laboratory and if patient is not on supplementary hormonal therapy) or surgically sterile (ie, tubal ligation, hysterectomy, bilateral salpingo-ophorectomy). See Section 7.2.7 for detailed requirements for WOCBP.
5. Male patients must agree to use an effective contraception method (eg, condom with spermicide) during the study, and continue to use this method for 1 week following their last dose of IMP or be congenitally or surgically sterile (eg, vasectomy with documented confirmation of post-surgical aspermia).

6. Must be willing and able to return for all clinic visits and to complete all study-required procedures.

Open-label Extension Period

7. Same as Double-blind Treatment Period Inclusion criteria, except the following modifications to Inclusion Criterion 2:
    a. ALT value can be normal or, if elevated, in the range of 1.25 to 10 times the ULN
    b. Inclusion Criterion 2b does not apply to the OLE Period
    c. Inclusion Criterion 2c must be met
8. Must have completed the Double-blind Period study visits through Week 24, including all Week 24 Visit assessments.
9. Must be willing to maintain glucocorticoid therapy or continue to taper glucocorticoid therapy as described in Section 6.2.2.1.

4.3. Exclusion Criteria

Only individuals who do not meet any of the following criteria may be enrolled in the study.

Double-blind Treatment Period

1. Have a concomitant diagnosis of primary biliary sclerosis, primary sclerosing cholangitis, IgG 4-related cholangitis, or drug-related AIH (at Screening) or a history of drug-related AIH.
2. Have clinical evidence of significant unstable or uncontrolled diseases other than the disease under study (eg, cardiac [including congestive heart failure, hypertension, angina, or myocardial infarction], pulmonary [including pulmonary hypertension or interstitial lung disease], hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurological, or infectious disease, any ongoing SAE(s), or AE(s) ≥ Grade 3 by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) that, in the opinion of the Investigator or Sponsor/designee, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence.
3. Are receiving oral or injectable immunomodulating treatment other than permitted concomitant medications in Section 6.2.3 prior to enrollment in the study. Patients who have been using such treatments must have had the washout periods outlined in Section 6.2.1.
4. Have an active infection (eg, acute hepatitis E, cytomegalovirus, or Epstein-Barr virus) requiring systemic therapy with antibiotic, antiviral, or antifungal treatment, or has had any febrile illness within 7 days prior to Day -1.
5. Have a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test (real-time polymerase chain reaction [RT-PCR]) at screening or Day 1.
6. Have a history of thyroiditis, celiac disease, or other autoimmune disorder known to be associated with transaminitis.
7. Have a history of primary or acquired immunodeficiency.

8. Have a history of malignancy of any type, with the exceptions of surgically excised nonmelanoma skin cancers, in situ cervical cancer >5 years prior to Baseline (Day 1), prostate cancer that is considered cured (normal prostate-specific antigen) for >5 years, colon cancer considered cured >5 years following surgical treatment, or lymphoma with >5 years complete remission.
9. Have a history of solid organ transplant.
10. Have a history of excessive alcohol use (consumption of 4 or more drinks on any day or 8 or more drinks per week for women and 5 or more drinks on any day or 15 or more drinks per week for men) or drug abuse in the 1 year prior to Screening, in the opinion of the Investigator.
11. Have an estimated glomerular filtration rate <60 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease (MDRD) equation (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]).
12. Have a hemoglobin level <9.0 g/dL, neutrophil count <1200/mm^3, or platelet count <120 × 10^9/L at Screening.
13. Have a prothrombin time above ULN at Screening, or an International Normalized Ratio (INR) >1.2.
    NOTE: Minor changes in coagulation parameters that may be attributable to permitted concomitant medications and that are not considered clinically significant by the Investigator are allowed.
14. Have a history of hypercoagulability (including, but not limited to, antiphospholipid antibody syndrome, activated protein C resistance, elevated coagulation factor VIII levels, sticky platelet syndrome, protein C or S deficiency, homocystinemia, antithrombin deficiency, dysfibrinolysis, or prothrombin G20210A mutation), thrombotic events (including, but not limited to, deep vein, femoral vein, superior vena cava, or jugular vein thrombosis; thrombotic stroke; pulmonary embolism; myocardial infarction; retinal vein occlusion, or thrombotic microangiopathies), or hemolytic uremic syndrome.
15. Have liver cirrhosis with significant impairment of liver function (Child Pugh category B or C), or have decompensated cirrhosis.
16. Patients with histology confirmed coincident non-alcoholic steatohepatitis. NOTE: Patients with other type of non-alcoholic fatty liver disease are NOT excluded from the study.
17. Have electrocardiogram (ECG) findings of QT corrected for pulse rate (QTcF) >480 msec, newly diagnosed (within 6 months prior to Screening) and/or poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant cardiac abnormalities.
18. Have positive serology results at Screening (human immunodeficiency virus [HIV], hepatitis B [surface antigen and core antibodies], hepatitis C [anti-HCV antibody confirmed with hepatitis C RNA]).
    - Patients who are hepatitis B virus surface antigen (HBsAg) positive will not be eligible.

- Patients who are HBsAg negative and hepatitis B core antigen antibody (HBcAb) positive will be tested for hepatitis B surface antibody (HBsAb) and hepatitis B DNA:
  - Patients with HBsAb titer ≥100 IU/L and negative hepatitis B DNA may be enrolled.
  - Patients with positive hepatitis B DNA results will be excluded.
  - Patients with HBsAb titer <100 IU/L or negative will be excluded.

19. Have positive interferon-gamma release assay (IGRA) (eg, T-SPOT tuberculosis [TB] Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus), at Screening, unless the patient has latent TB and all of the following are true:
    - The chest X-ray does not show evidence suggestive of active TB.
    - There are no clinical signs or symptoms of pulmonary and/or extra-pulmonary TB.
    - The patient has documented evidence of receiving one of the following prophylactic treatment regimens: daily oral isoniazid for 6 months, daily oral rifampin for 6 months, or isoniazid and rifapentine weekly for 3 months.

    Note: If a QuantiFERON®-TB Gold/Gold Plus is indeterminate for any reason and a T-SPOT TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor. On a case-by-case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to one of the above tests may be used for eligibility. Without a negative test, unless treated as noted above, one or more indeterminant tests are not sufficient for the patient to be enrolled (see Section 7.2.4.5.1.1).
20. Have taken rituximab, other B- or T-cell depleting agents, or alkylating agents within 6 months of screening, unless B- or T-cells have been shown to return to normal values (B-cells [CD19+] >100 cells/μL; T-cells [CD4+] >500 cells/mm^3).
21. Require regular use of medications with known hepatotoxicity (see Section 6.2).
22. Have previously used a proteasome inhibitor (dual proteasome inhibitors allowed if it has been at least 1 year since last use).
23. Have received a live vaccine within 28 days prior to Baseline (Day 1), or plan to receive a live vaccine during the study.
24. Have used another investigational medical therapy, and/or participated in an investigational trial within 6 months or 5 half-lives (whichever is longer) prior to Screening.
25. Are females who are breastfeeding or who plan to become pregnant during the study, or who are actively trying to conceive at the time of signing of the informed consent form (ICF).
26. Have known hypersensitivity to zetomipzomib or any of its excipients.

Open-label Extension Period

27. Same as Double-blind Treatment Period exclusion criteria. No need to re-test for antiphospholipid antibody, HIV, HBV, HCV, and TB.

5. STUDY TREATMENT INFORMATION

Instructions for the receipt, inspection, storage, preparation, administration, and disposal of IMP will be provided in a separate Pharmacy Manual at each site.

5.1. Physical Description of Investigational Medicinal Product

Active IMP (zetomipzomib) is supplied as sterile lyophilized solids in single-use glass vials. Each vial is reconstituted with sterile WFI diluent prior to administration. Details of the zetomipzomib drug product formulation are provided in the Investigator's Brochure.

Placebo control will consist of sterile WFI in an equivalent volume to the reconstituted zetomipzomib dose.

Commercially available sterile WFI may be used as diluent for active IMP reconstitution and as placebo. Commercially available sterile WFI should be stored as per the manufacturer's recommendation.

5.2. Packaging and Labeling

Active IMP will be packaged in cartons. All active IMP will be manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) and relevant regulatory guidelines. All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practice (GMP) and relevant regulatory requirements.

5.3. Supply, Dispensing, Storage, and Investigational Medicinal Product Accountability

Refer to the most current version of the Investigator's Brochure and Pharmacy Manual for storage conditions for active IMP. The current recommended storage condition for active IMP is 2°C to 8°C.

Upon receipt of active IMP, the Investigator (or designee) will conduct an inventory of the supplies and verify that they are received in acceptable condition and in the correct amounts. The Clinical Site Monitor (Monitor) may verify the study supplies at each study center at any time during the study.

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all active IMP received and that any discrepancies are reported and resolved before use of the active IMP.

Only patients enrolled in the study may receive IMP. All IMP should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions. Unless communicated as permissible by Sponsor, excursions from labeled storage conditions must be reported and resolved before use. Access to IMP must be limited to the investigator and authorized site personnel.

The Investigator or the head of the medical institution (where applicable) is responsible for accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records) of IMP. It is the responsibility of the Monitor to ensure that the Investigator (or designee) has correctly documented the amount of IMP received, dispensed, and returned in a

dispensing log. A full accountability log will be maintained at the site at all times. The Monitor will perform an inventory of IMP at the closeout visit to the site. All discrepancies must be accounted for and documented.

6. DOSAGE AND STUDY MEDICATION ADMINISTRATION

6.1. Investigational Medicinal Product Administration

An unblinded Pharmacist will prepare and blind the active and placebo doses. During the Double-blind Treatment Period, IMP (active zetomipzomib or volume-matched placebo) will be administered by SC injection once weekly, according to randomization. The first dose will be 30 mg zetomipzomib or placebo, administered at the clinical trial site, followed by weekly doses of 60 mg zetomipzomib or placebo for the remaining 23 weeks of the Double-blind Treatment Period. During the OLE Period, zetomipzomib will be administered to all patients by SC injection once weekly. The first open-label dose will be 30 mg zetomipzomib, followed by weekly doses of 60 mg zetomipzomib for the duration of the OLE Period.

After the first dose, IMP will be administered by study personnel at the site or by a home trial service at the patient's home or alternate location (eg, place of employment).

Weekly doses will be administered according to the Schedules of Assessments (Table 1 through Table 4).

Further details regarding drug product formulation, preparation, and administration of IMP will be provided in a separate Pharmacy Manual.

6.1.1. Administration Site

SC injection sites should be rotated (eg, 4 abdominal quadrants, posterior upper arms, anterior thighs), and a minimum of 4 weeks should separate injections to the same anatomic site, if possible.

6.1.2. Suggested Measures to Improve Investigational Medicinal Product Tolerance

Initial SC administration of zetomipzomib at doses of 60 mg or above is occasionally associated with at least one of the following signs/symptoms: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors and/or chills. These signs/symptoms typically begin within 8 to 24 hours after dosing, and usually resolve within 48 hours after dosing.

Although the numbers are small, the percentage of patient reporting TEAEs of the above signs/symptoms appears to be lower in patients who received zetomipzomib as step-up doses and/or with pre-/post-dose prophylaxis, suggesting that these methods are effective at tolerizing patients to higher doses of zetomipzomib.

Step-up Dosing

All patients will receive an initial SC step-up dose of 30 mg zetomipzomib or placebo, followed weekly by the target dose of 60 mg SC zetomipzomib or placebo.

Pre/Post Dose Prophylaxis

Prophylactic measures may be considered if any of the signs and/or symptoms listed above develop, and may be used as treatment. Measures that have been demonstrated to reduce the incidence and severity of SC administration-related reactions include the following:

- Fluid hydration, eg, 250-500 mL oral (or IV if necessary) of an electrolyte solution up to 48 hours prior to dosing, or up to 24 hours after dosing if symptoms are present
- Antiemetics, non-sedating antihistamines, and/or acetaminophen are permitted if patients are prone to specific symptoms.

If additional guidance for improving initial tolerability symptoms is required, the Medical Monitor should be consulted. Home trial service providers do not provide or administer any of the fluids or medications listed above.

6.1.3. Dose Modification Guidelines

6.1.3.1. Dose Reduction

If the Investigator is concerned that a patient needs a dose reduction due to safety or tolerability, the Medical Monitor should be consulted for a reduction of IMP. The dose may then be reduced to a 45 mg or 30 mg dose of zetomipzomib or placebo in a blinded manner during the Double-blind Treatment Period, or to a 45 mg or 30 mg dose of zetomipzomib during the OLE Period.

Written approval from the Medical Monitor should be obtained in advance of implementing dose reduction, when possible. After dose reduction is implemented, patients should remain on the reduced dose for at least 2 doses, after which the dose may be re-escalated to a 60 mg dose of zetomipzomib or placebo. If the 60 mg zetomipzomib or placebo dose is not tolerated after re-escalation, the reduced dose may be continued for the remainder of the study, or re-escalation to a 60 mg dose of zetomipzomib or placebo may be re-attempted after written approval from the Medical Monitor. Any dose modifications should be documented in the electronic case report form (eCRF) as per Section 9.1.4.

6.1.3.2. Missed Doses

Doses should be administered within the visit windows as per the Schedule of Assessments (Section 7.1). Any doses administered outside of the visit window will be considered a protocol deviation; however, if necessary to avoid missing a dose, doses may be administered up to 3 days from the date of scheduled administration with a minimum of 4 days required between doses.

Patients who meet individual patient stopping rules (Section 8.1.2) may resume dosing after discussion between the Investigator and Medical Monitor. Upon resumption of dosing, subsequent doses should be timed according to the original dosing schedule based on Day 1. Missed doses should be documented in the eCRF as per Section 9.1.4. Patients who are discontinued for missed doses should have their discontinuation recorded in the eCRF based on the reason the doses were missed, eg, AE, protocol noncompliance. The Investigator should contact the Medical Monitor if a patient misses >2 consecutive doses or >4 total doses to determine whether the patient should resume administration of IMP.

If IMP is permanently discontinued due to an AE, the planned assessments (see Schedule of Assessments in Table 1 and Table 3) should continue for the protocol-specified time period. If the patient cannot continue with the planned assessments, the patient will complete the ETV (Table 3) followed by the safety follow-up (EOS) visit (Table 3) 4 weeks later.

6.2. Prior and Concomitant Treatments

A concomitant medication is any prescription or over-the-counter preparation, including vitamins and supplements. A concomitant therapy is any therapy that may be used, eg, physical therapy, surgery, or medication. Except as described in Section 6.2.1, prior and concomitant medications and therapies will be recorded on the eCRF for 60 days prior to Screening and continuing for 30 days following the last dose, or the EOS visit, whichever occurs later. Details to be recorded include, but are not limited to, the concomitant medication generic name, dose, route, frequency of administration, and indication.

6.2.1. Prior Treatment Restrictions

All prior AIH treatments (eg, glucocorticoids, immunosuppressants, antimalarials, and biologics) will be recorded, from at least 24 weeks prior to Screening. When possible, all prior biologics should be recorded. Details to be recorded include, but are not limited to, the concomitant medication generic name, dose, route, frequency of administration, and indication. Patients taking immunologic response modifiers must have completed the washout periods shown below prior to enrolling in the study.

≥2 weeks prior to Screening:	Methotrexate, dapsone, intravenous immunoglobulin, anakinra, etanercept, sirolimus, or any other immunosuppressant not elsewhere mentioned
4 weeks prior to Screening	Thioguanine
12 weeks prior to Screening:	Infliximab, adalimumab, golimumab, abatacept, tocilizumab, certolizumab, secukinumab, plasmapheresis
6 months prior to Screening:	Anti-CD20 drugs such as rituximab, ofatumumab, or other long-acting biologics, proteasome inhibitors such as carfilzomib or bortezomib

A shorter washout period is allowed for anti-CD20 treatments if there is documented B cell reconstitution.

6.2.2. Required Concomitant Medications and Therapies

6.2.2.1. Glucocorticoids

Oral prednisone/prednisone equivalent is a required concomitant medication during this study. Enteric-coated glucocorticoids are not permitted. Patients will take their own supply of glucocorticoids. Patients should be informed of and follow appropriate local practice for this medication including monitoring for adverse effects.

Enrolled patients will be on standard-of-care with a prednisone/prednisone equivalent dose of 20 mg/day on Day 1 (Visit 2). Following consultation with the Medical Monitor, patients who are taking a prednisone/prednisone equivalent dose higher than 20 mg/day at Day 1 may also be enrolled in the study provided the prednisone/prednisone equivalent dose does not exceed 40 mg/day. For the Double blind Treatment period, patients are encouraged to undergo a glucocorticoid taper of prednisone/prednisone equivalent dose according to the

protocol-suggested glucocorticoid taper schedule (Table 6) and prednisone equivalent doses (Table 7) as provided in Appendix B Patients taking budesonide who are unwilling to switch to a prednisone/prednisone equivalent for the study may continue to take budesonide at the doses shown in Appendix B. For suggested glucocorticoid taper schedule, please see Appendix B.

During the glucocorticoid taper, patients with signs and symptoms of worsening disease (ie, worsening of ALT level ≥25% from Baseline for ≥1 week, as verified via repeat laboratory assessments) may increase glucocorticoid doses following consultation with the Medical Monitor.

During the OLE Period, prednisone/prednisone equivalent can continue to be tapered and may be withdrawn (see Appendix B for suggested taper schedule). Investigators are encouraged to further taper to discontinuation if clinically appropriate throughout the study, particularly during the OLE Period.

6.2.3. Permitted Concomitant Medications and Therapies

Concomitant therapies for comorbid conditions are permitted; these therapies should be recorded in the eCRF. Details regarding physical therapy, occupational therapy, or exercise should also be recorded in the eCRF.

Concomitant use of cholesterol lowering medications (ie, statins) at prescribed doses and acetaminophen (Tylenol®) below 4,000 mg per day during the study are permitted if the patient's elevated ALT level is not related to the use of these medications in the Investigator's opinion.

Concomitant medications in the following subsections are allowed throughout the study as described in Section 3.1.1.

6.2.3.1. Azathioprine (AZA)

Patients who are taking AZA in addition to prednisone/prednisone equivalent as part of their usual care may continue, but no more 150 mg per day (Mack et al., 2020). The AZA dose is to be held constant unless tolerability/AEs require dose adjustment, or decreased after completion of glucocorticoid taper, at the Investigator's discretion. Evolving leukopenia or thrombocytopenia warrants dose reduction or drug withdrawal. AZA should be discontinued if the cytopenia does not recover in 1-2 weeks.

6.2.3.2. Inhibitors of Inosine Monophosphate Dehydrogenase (Mycophenolate Mofetil [MMF], Mycophenolate Sodium [MMS] and Mycophenolic Acid [MPA])

Patients who are taking MMF or equivalent, such as mycophenolic acid and mycophenolate sodium, in addition to prednisone/prednisone equivalent as part of their usual care may continue, and the dose is to be held constant unless tolerability/AEs require dose adjustment, or decreased after completion of glucocorticoid taper, at the Investigator's discretion. Twice daily, 3 times daily, or 4 times daily (if needed due to gastrointestinal AEs) dosing are permitted. Doses of MMF or equivalent from 1 g/day to 3 g/day are permitted per the Investigator's discretion.

6.2.3.3. Tacrolimus (TAC)

Patients who are taking oral TAC in addition to prednisone/prednisone equivalent as part of their usual care may continue, and the dose is to be held constant unless tolerability/AEs require dose

adjustment, or decreased after completion of glucocorticoid taper, at the Investigator's discretion. Doses from 1 mg/day to 8 mg/day are permitted per the Investigator's discretion (Efe et al., 2017).

6.2.3.4. Cyclosporine A (CsA)

Patients who are taking oral CsA in addition to prednisone/prednisone equivalent as part of their usual care may continue, and the dose is to be held constant unless tolerability/AEs require dose adjustment, or decreased after completion of glucocorticoid taper, at the Investigator's discretion. Doses from 1 to 2 mg/kg body weight, twice a day, are permitted per the Investigator's discretion (Nasseri-Moghaddam et al., 2013).

6.2.3.5. 6-Mercaptopurine (6-MP)

Patients who are taking oral 6-MP in addition to prednisone/prednisone equivalent as part of their usual care may continue, and the dose is to be held constant unless tolerability/AEs require dose adjustment, or decreased after completion of glucocorticoid taper, at the Investigator's discretion. Doses from 25 to 50 mg/day or more if therapy is tolerated, are permitted per the Investigator's discretion (Hübener et al., 2016).

6.2.4. Prohibited Concomitant Medications

Concomitant use of any immunosuppressant medication other than glucocorticoids and AZA, MMF or equivalent, TAC, CsA, or 6-MP during the study is prohibited (eg, those listed in Section 6.2.1). Patients who need other immunosuppressant therapy during the study should be withdrawn from study participation. In addition, concomitant medications associated with AIH (eg, minocycline, allopurinol, nitrofurantoin) are prohibited.

6.2.5. Potential Drug-Drug Interactions

Zetomipzomib has a half-life of ~5 hours in humans and is metabolized extra-hepatically by the ubiquitously expressed epoxide hydrolase. A very weak inhibition of CYP-Pg has been observed but is unlikely to be of clinical significance. No drug-drug interactions are predicted, but all efforts will be made to observe if any occur.

6.2.6. Vaccinations

Zetomipzomib is not anticipated to impact the response to vaccinations. It is strongly recommended that patients be up to date on immunizations per current AASLD guidelines (Mack et al., 2020) prior to Screening. If vaccinations are recommended and received during the study, they should be recorded in the eCRF. Live vaccinations are not permitted during the study. If vaccination against herpes zoster is required during the study, Shingrix or other non-live vaccine (if available) is preferred over live vaccines. Similarly, vaccination against influenza virus with inactivated vaccine is preferred. If a patient requires the vaccine against coronavirus disease 2019 (COVID-19) during the study, no interruption of IMP treatment is required for the purpose of vaccination. If it is possible to schedule COVID-19 vaccine administration with respect to IMP administration, the following is recommended when feasible:

- If IMP is administered in an extremity, the vaccine should be administered in an extremity other than the one used for IMP injection that week.
- If symptoms related to IMP administration are present, it is recommended to time the administration of the vaccine when the symptoms are resolved or resolving
- For patients who have received at least 3 doses of IMP, ideally 2 days should separate administration of IMP and the vaccination to permit sufficient time to distinguish potential adverse effects.
- For patients who have received less than 3 doses of IMP, ideally 3 days should separate administration of IMP and the vaccination to permit sufficient time to distinguish potentialadverse effects.

6.2.7. Other Restrictions and Prohibitions

For patients requiring surgery, or for any planned surgery during the study, the Medical Monitor should be consulted to discuss IMP dosing.

6.3. Rescue Therapy

Rescue therapy is defined as any modification to the background AIH treatment, including dose or frequency increases in concomitant medications or initiation of a new medication. Rescue medications may include, but are not limited to systemic glucocorticoids, AZA, MMF, calcineurin inhibitor, and other immunosuppressants according to the guideline (Mack et al., 2020). While rescue therapy is typically restricted or prohibited per protocol (Section 6.2.4), patients may receive rescue therapy during the study at the discretion of the Investigator when deemed medically necessary for the safety of the patient. Examples of situations that might require rescue therapy include:

- Patients who meet the definition for treatment failure or disease flare that requires higher than the maximum protocol-allowed prednisone/prednisone equivalent dose (Section 3.1) or addition of other immunosuppressant medication(s)
- Patients requiring hospitalization due to signs of acute liver failure
- Patients with evidence of a coagulation abnormality (eg, INR ≥1.5)
- Patients with any degree of mental alteration (encephalopathy) without pre-existing cirrhosis and with an illness of <26 weeks duration (Polson et al., 2005).

If an Investigator determines that a patient needs rescue therapy, the Medical Monitor should be informed; where possible, a discussion should occur between the Investigator and Medical Monitor prior to implementation of the rescue therapy. Any rescue medications administered should be recorded in the eCRF under concomitant medications. Patients who receive rescue therapy will temporarily discontinue IMP, complete the Double-blind Period visits, and remain eligible for the OLE Period.

7. STUDY EVALUATIONS

7.1. Schedule of Assessments

7.1.1. Double-blind Treatment Period

The Schedule of Assessments is presented in Table 1, and the Schedule of IMP Administration (for visits at which no assessments are scheduled) is presented in Table 2.

Screening assessments should be performed between Day -28 and Day -1. The Screening period may be extended to 35 days upon approval by the Sponsor or designee. Patients who do not meet inclusion/exclusion criteria may be rescreened one time.

Study visits will occur according to Table 1 and Table 2. Glucocorticoid tapering will be evaluated from the Week 2 visits.

At on-site study visits, safety and efficacy assessments will be performed and IMP will be administered according to the Schedule of Assessments (Table 1). All other study visits may occur either at the site or at patients' homes or alternate location (eg, place of employment) via home trial service (Table 2).

7.1.2. Open-label Extension Period

At on-site study visits, safety and efficacy assessments will be performed and IMP will be administered according to the Schedule of Assessments (Table 3). All other study visits may occur either at the site or at patients' homes or alternate location (eg, place of employment) via home trial service (Table 4).

For patients who roll over immediately to the OLE Period, Study Visit 26 (Table 1) may occur on the same day as Study Visits 27 and 28 (Table 3). For patients who initiate the OLE Period within 4 weeks after the Week 24 Visit of the Double-blind Treatment Period, the most recently reported assessments from Week 20 or later in the Double-blind Treatment Period may serve as the eligibility assessments for the OLE Period (ie, OLE Visit 27 assessments do not need to be repeated). For patients who roll into the OLE Period >4 weeks and <12 weeks after the Week 24 Visit of the Double-blind Treatment Period, Visit 27 assessments must be performed within 28 days prior to first open-label IMP administration to confirm eligibility for the OLE.

7.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for other reasons, as warranted. During an unscheduled visit, information regarding concomitant medications and AEs (at a minimum) will be collected. Any of the other procedures listed for the Week 24 visit may also be performed at the Investigator's discretion.

7.1.4. Telehealth Visits

While the study visits in Table 1 and Table 3 are mandatory, in the event of constraints imposed by the COVID-19 pandemic, sites may elect to use a combination of telemedicine (as permitted by their institutions) and/or home trial service to conduct these visits. Weekly IMP injections

listed on Table 2 and Table 4 may occur at the site or at patients' homes or alternate location (eg, place of employment) via home service.

For telehealth visits, weight will not be measured, and a limited physical examination will be performed. All other assessments should be performed, if feasible. Samples for clinical laboratory assessments will be collected by home trial service providers and sent to the central laboratory.

7.2. Study Procedures and Assessments

All patients must be provided an ICF describing the study with sufficient information for them to make an informed decision regarding their participation as per Section 11.3. Informed consent must be signed prior to any procedures for the study. All study procedures and assessments should be performed according to the schedules presented in Table 1 through Table 4.

If a patient is not able to come to the site for an on-site visit as per the Schedule of Assessments (Table 1 and Table 3), a telehealth visit should occur (see Section 7.1.4).

7.2.1. Medical History

Documentation of the patient's medical history should contain the patient's full medical history including past and concomitant illnesses/diseases, year of diagnosis, date and results of liver biopsy or biopsies, prior and concomitant medications, demographic data (race, ethnicity, date of birth, and gender), and social history (tobacco use, drugs of abuse, and alcohol use).

7.2.2. Efficacy Assessments

Efficacy assessments will be performed for all patients, unless indicated otherwise, at the visits shown in the Schedule of Assessments (Table 1 and Table 3).

7.2.2.1. Aminotransferases and Immunoglobulin G

ALT, aspartate aminotransferase (AST) and IgG will be collected as part of the clinical laboratory assessments (see Section 7.2.4.5) and used for analysis of the related efficacy endpoints.

7.2.2.2. Vibration-controlled Transient Elastography

Liver stiffness will be assessed using a Fibroscan® ultrasound device, which is a non-invasive method of determining liver fibrosis. The test will be performed on an empty stomach, at least 2 hours after food intake. The patient will be instructed to lie supine. An ultrasound-like probe will be placed on the skin over the liver area, typically in the right mid-axillary line. The liver fibrosis stage will be assessed using the liver stiffness measurement (LSM) scores recorded as kilopascal (kPA) as well as controlled attenuation parameter (CAP) recorded as decibels/meter (dB/m), which is a marker of hepatic steatosis, graded as 0, 1, 2 and 3 (Siddiqui et al., 2019).

7.2.2.3. Liver Histopathology

If a liver biopsy is not available from within 6 months prior to Screening, a liver biopsy sample will be collected at Screening. Local reports of the liver biopsy are sufficient for inclusion. Results from a liver biopsy with Ishak histological grading and staging scores (Ishak et al., 1995)

performed at Screening or within 6 months prior to Screening will be used as the Baseline for comparison with the liver biopsy collected at Week 24 of the Double-blind Treatment Period as well as the optional liver biopsy collected at OLE Week 25. Review of liver biopsies will be done at a local laboratory. A central review of liver biopsies may also be performed as an optional exploratory analysis.

7.2.2.4. Glucocorticoid Toxicity Index

The GTI is a comprehensive, outcome-based glucocorticoid toxicity-monitoring instrument developed by a multidisciplinary team of international experts (Jayne et al., 2021).
The instrument calculates a composite index score from data captured related to the following domains: body mass index, glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. In addition, reports of any of the following toxicities are included in the index: endocrine (adrenal insufficiency), gastrointestinal (perforation, peptic ulcer disease), musculoskeletal (ruptured tendon, avascular necrosis), and ocular (retinopathy, increase in ocular pressure, posterior subcapsular cataract).

The GTI instrument uses 2 GTI scores: the Cumulative Worsening Score and the Aggregate Improvement Score, referred to as GTI-CWS and GTI-AIS, respectively.

7.2.3. Patient Reported Outcome Measures

7.2.3.1. EuroQol 5-Dimension 5-Level

The EQ-5D-5L is a standardized instrument developed by the EuroQoL Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system and the EuroQol visual analog scale (EQ-VAS).

The descriptive system comprises 5 levels of severity for each of 5 dimensions (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-VAS records the patient's self-rated health on a vertical visual analog scale. This can be used as a quantitative measure of health outcome that reflects the patient's own judgment. The scores on these 5 dimensions can be presented as a health profile or converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

7.2.3.2. Chronic Liver Disease Questionnaire

The CLDQ is the most widely validated disease-specific health-related quality-of-life instrument for patients with chronic liver disease (Younossi et al., 1999). It has been cross-culturally validated and translated, and has demonstrated validity and reliability in patients with chronic liver disease across a variety of cultural and socioeconomic differences. The CLDQ produces both a summary score and domain score, and correlates with the severity of liver disease.
The instrument contains 29 items within 6 domains including abdominal symptoms (items 1, 5, 17), fatigue (items 2, 4, 8, 11, 13), systemic symptoms (items 3, 6, 21, 23, 27), activity (items 3, 6, 21, 23, 27), emotional function (items 10, 12, 15, 16, 19, 20, 24, 26) and worry (items 18, 22, 25, 28, 29). A Likert scale response format is used for all items ranging from 1 (most impairment) to 7 (least impairment). Scoring of the questionnaire is performed by dividing each domain score by the number of items per domain (Younossi et al., 1999).

7.2.4. Safety Assessments

Safety will be assessed throughout the study by monitoring of vital signs, ECG, physical examinations, and laboratory tests; and by recording and analyzing all AEs and SAEs.

7.2.4.1. Vital Sign Measurements

Blood pressure, pulse rate, respiratory rate, and temperature will be measured at the visits shown in the Schedules of Assessments (Table 1 and Table 3). Blood pressure and pulse rate should be collected after the patient has had at least 5 minutes of rest in the seated position. If the blood pressure is elevated on the first measurement at Screening, it should be repeated after at least an additional 5 minutes of rest. It is recommended that blood pressure is measured using the same arm at each assessment. When the time of vital signs measurement coincides with a blood sample collection, the vital signs will be measured before blood sample collection.

7.2.4.2. Electrocardiograms

A 12-lead ECG will be performed at the on-site visits specified on the Schedule of Assessments (Table 1 and Table 3). The ECG should be performed after the patient has rested for at least 5 minutes in a supine position.

The Investigator or qualified designee will review and indicate whether the ECG is normal or abnormal, specify the abnormality, and whether clinically significant. Any clinically significant ECG result will be recorded as medical history or an AE per the Investigator's judgement.

7.2.4.3. Weight and Height

When possible, body weight will be recorded as part of the full physical examination at the on-site visits shown in the Schedule of Assessments (Table 1 and Table 3). Body weight, with the patient wearing light clothing and the shoes and jacket or coat removed, will be measured and recorded in kilograms.

Height will be measured at Visit 2 only.

7.2.4.4. Physical Examination

Complete physical examinations will be performed at the on-site visits specified on the Schedule of Assessments (Table 1 and Table 3). A complete physical examination should include assessments of at least the following: general appearance, skin, head, ears, eyes, nose and throat, heart, chest/breast, abdomen, neurological system (briefly), lymph nodes, spine, and skeletal extremities.

At other visits (including other on-site visits and unscheduled visits), an abbreviated physical examination, symptom-directed as determined by the Investigator, may be performed to include general appearance, cardiovascular, gastrointestinal, and pulmonary systems. Medically significant changes from physical examination will be recorded as AEs.

7.2.4.5. Clinical Laboratory Assessments

Clinical laboratory tests for safety, including hematology, clinical chemistry, immunoglobulins, autoantibodies, and clinical laboratory assessments for efficacy measures will be performed at a central laboratory at the visits shown on the Schedules of Assessment (Table 1 and Table 3).

Hematology: complete blood count with differential

Coagulation: prothrombin time, INR, activated partial thromboplastin time, antiphospholipid antibodies (Screening only)

Clinical chemistry: Non-fasting chemistry panel including electrolytes, AST, ALT, alkaline phosphatase (ALP) and total bilirubin; lactate dehydrogenase, blood urea nitrogen (BUN), albumin, total protein, creatinine, glucose, low-density lipoproteins (LDL), amylase, lipase, triglycerides, hemoglobin A1c (HgbA1c), and C-reactive protein.
LDL, ALP, amylase, lipase, triglycerides, and HgbA1c are only required at Day 1 (pre-dose) and Week 24 of the Double-blind Treatment Period, and OLE Week 25.

IgG: Immunoglobulin G

Autoantibodies: Antinuclear antibodies (ANA), smooth muscle antibody (SMA), liver kidney microsome type 1 (anti-LKM-1) antibody, anti-liver cytosol type 1 (LC1) antibodies, anti-soluble liver antigen/liver pancreas (SLA/LP) antibodies

Urinalysis: macroscopic and microscopic examination

Additional blood will be sent for biomarker studies as per Section 7.2.5.

Unscheduled or additional laboratory samples may be collected and analyzed by local laboratories if immediate results are necessary for management of TEAEs or dosing determination. Urine pregnancy tests will be performed locally.

Unless otherwise noted, when scheduled simultaneously with a dosing visit, samples for laboratory evaluations should be collected prior to administration of IMP.

Clinical laboratory results the Investigator deems clinically significantly abnormal should be repeated within 48 to 72 hours from when the result became available, when possible.

7.2.4.5.1. Infectious Disease Blood Tests

Infectious disease blood tests screening for HBsAg, HBcAb, hepatitis C antibody, and HIV will be performed at Screening only. Positive screening results may require additional testing.

For HBcAb-positive patients permitted to enter the study (HBcAb positive, HBsAg negative, HBsAb titer ≥100 IU/L, and negative hepatitis B DNA), additional assessments for hepatitis B DNA will be performed as described in Inclusion Criterion 18 (Section 4.3).

7.2.4.5.1.1. Tuberculosis Test

Evaluation of all patients by QuantiFERON®-TB Gold/Gold Plus test will be performed by the central clinical laboratory. On a case-by-case basis upon approval by the Sponsor, negative results on a local TB test that is considered equivalent to one of the above tests may be used for eligibility. Use of the T-SPOT® TB test will also be permitted locally.

Latent TB: If the Screening QuantiFERON-TB Gold/Gold Plus (or a local T-SPOT TB) test is negative and there is no known history of recent exposure to individuals with active TB and the chest x-ray shows no evidence of active TB, the patient may be enrolled. If the Screening QuantiFERON-TB Gold/Gold Plus test is positive and/or the patient is diagnosed with latent TB, they must have a chest x-ray that shows no evidence of active TB, no clinical signs and

symptoms of TB, and documentation confirming completion of appropriate prophylactic treatment prior to being permitted to enroll.

An indeterminate QuantiFERON-TB Gold/Gold Plus test at Screening must be repeated at least once as soon as possible by the central laboratory (QuantiFERON-TB Gold/Gold Plus test) or local laboratory (QuantiFERON-TB Gold/Gold Plus or T-SPOT TB). If the result remains indeterminate (or borderline on T-SPOT TB test), the patient is not eligible for enrollment into the study, unless already treated for latent TB as described above for a positive test. The site, if it has performed the T-SPOT TB test locally and if it has the appropriate equipment and laboratory kits, may perform the QuantiFERON-TB Gold Plus test centrally if a repeat test needs to be performed.

7.2.5. Exploratory Assessments

Additional blood and plasma will be collected and may be sent for biomarker studies. Biomarker assessments may be reported separately. Detailed instructions for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

7.2.5.1. Cytokines and Proteomics

Plasma samples will be collected at the times shown in the Schedule of Assessments (Table 1 and Table 3) for the measurement of cytokines and other circulating proteins by electrochemiluminescent (Meso Scale Discovery) or enzyme-linked immunosorbent assay (ELISA). Blood samples will be collected for immune cell profiling performed by flow cytometry. Samples for proteomics and immune cell profiling will be stored for future analysis of chemokines and immune cell subsets. Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

7.2.5.2. Genotyping and Gene Expression

Gene expression (ribonucleic acid [RNA]) profiling and DNA genotyping may be assessed in blood samples. A whole blood sample will be collected for gene expression analysis for storage and analysis at a later date as specified in the Schedule of Assessments (Table 1 and Table 3) and to the extent permitted by the national and/or local laws and regulations.

Samples will be used to conduct retrospective disease or population genetic research as a separate analysis not included in this study. Samples may be used to investigate variable response to zetomipzomib and to investigate genetic or epigenetic variants thought to play a role in the diseases under investigation in this study. Assessment of variable response may include evaluation of AEs or differences in efficacy. The results may be reported in the separate report.

Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

7.2.6. Pharmacokinetic Assessments

Blood samples will be collected from all patients during the Double-blind Treatment Period according to the Schedule of Assessments (Table 1). Samples will be used to measure the plasma concentration of zetomipzomib and its metabolite KZR-59587 (AUC, C_{max}, T_{max}, and other

PK calculations). Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

Samples collected to measure investigational product concentration and metabolism will be retained for as long as legally permitted in the country of origin or until Sponsor decision to destroy.

Measures will be in place at the Sponsor to prevent unblinding by laboratory measurements.

7.2.7. Contraception Requirements and Pregnancy Testing

WOCBP must agree to use highly effective and medically acceptable methods of contraception to prevent pregnancy during the study and for 4 weeks after administration of the last dose of IMP. For the purposes of this study, WOCBP are defined as fertile female patients, unless the patient is postmenopausal (defined by amenorrhea for at least 2 years or amenorrhea for at least 1 year with confirmatory FSH level in the postmenopausal range, as documented historically or measured by the central or local laboratory and if patient is not on supplementary hormonal therapy) or surgically sterile (ie, bilateral tubal ligation, hysterectomy, bilateral salpingo-ophorectomy).

Highly effective contraception is defined as the use of an intrauterine device or hormonal contraceptives (eg, implant or oral) or having a vasectomized partner. In regions where it is considered highly effective contraception, 2 barrier methods (eg, female diaphragm and male condom OR 1 barrier method with spermicide) may be used.

If using a hormonal form of contraception, use must have been stable for at least 4 weeks prior to the Baseline (Day 1), and if using concomitant mycophenolate, the patient must use another highly effective nonhormonal form of contraception. Abstinence will be acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation) and withdrawal are not acceptable methods of contraception.

For WOCBP, urine pregnancy testing will be performed at the time points shown in Table 1 and Table 3. IMP should not be administered prior to confirmation of a negative test at visits at which pregnancy tests are performed. Positive urine pregnancy tests should be confirmed by a serum pregnancy test.

Samples for FSH testing may be collected at any time during the study to confirm postmenopausal status in female patients whose childbearing potential status has changed since the Screening Visit. Only after confirmation of postmenopausal status is pregnancy testing not required.

Male patients must use an effective contraception method (eg, condom with spermicide) during the study, and continue to use the method for 1 week following the last dose of IMP or be congenitally or surgically sterile (eg, vasectomy with documented confirmation of post-surgical aspermia). The requirement for 1 week of post-treatment contraception for male patients is supported by the short half-life of zetomipzomib (<2 hours), full recovery of immunoproteasome inhibition within 3 days of dosing, lack of mutagenic potential as determined in vitro and in vivo nonclinical studies, and lack of reproductive organ findings in the 6- and 9-month rodent and monkey repeat-dose toxicity studies. Additionally, no teratogenic effects were found in the definitive embryofetal toxicity studies in rats and rabbits. As per International Council for Harmonisation (ICH) M3 (R2) guidance, lack of reproductive and teratogenic findings in general

toxicity and embryofetal toxicity studies is sufficient to support the treatment of male patients in Phase 1 and 2 trials prior to conducting fertility studies.

8. STUDY DISCONTINUATION

The Investigator must make every reasonable effort to keep each patient on study for the duration of the study, including through the safety follow-up, lost to follow-up (see Section 8.2 for additional details), consent withdrawal, or end of study, whichever occurs first.

8.1. Study and Individual Patient Stopping Rules

8.1.1. Termination or Suspension of the Study

The Sponsor has the right to terminate the study at any time, for any reason, including safety or administrative reasons. In all cases, all necessary measures will be taken to guarantee appropriate safety follow-up of patients already included in the trial. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory, and the Sponsor wishes to stop the study.
- IDMC recommendation due to safety concerns.

The IDMC will hold periodic meetings to undertake thorough reviews of the accumulated safety data. The IDMC can recommend stopping the study based on their review and findings (see Section 9.11). Further information about the IDMC's role and oversight will be detailed in the IDMC charter.

In the event that the Sponsor terminates the study, Investigators will be informed of the reason for study termination. Should the study be terminated due to safety reasons, the Investigator must contact all study patients promptly, complete the EOS procedures, and return the IMP.

8.1.2. Individual Patient Stopping Rules

The Investigator and Sponsor may discontinue the patient from study participation at any time if discontinuation would be in the patient's best interest. If a patient meets any of the stopping criteria listed below, the patient will complete the assessments for the EOT Visit and return 4 weeks after the last dose for the EOS Visit. Reasons for discontinuing a patient are not necessarily limited to the criteria below.

- Development of AIH manifestations or intercurrent liver disease (eg, viral hepatitis) while on IMP that threaten the patient's life or liver function (ie, AST, ALT or total bilirubin values ≥10 × ULN that has been verified via repeat laboratory assessment and is sustained for ≥1 week)
- Grade 4 (life-threatening) TEAE, unless due to an obvious alternative etiology
- Serious allergic reaction to IMP, including anaphylaxis
- Confirmed thrombotic microangiopathy (TMA)
- HIV/acquired immune deficiency syndrome (AIDS), viral hepatitis (B and C) infection occurring during the study
- Pregnancy

- Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the patient to risk if the patient continues with IMP or that prevents the patient's adherence to the protocol
- Protocol deviation involving inclusion or exclusion criteria that, in the Investigator's and Sponsor's judgment, would significantly compromise data interpretation or patient safety
- Investigators should grade and report injection site reactions (ISRs). If a patient develops a CTCAE Grade ≥3 ISR, or if a Grade 2 ISR worsens, the patient's IMP will be discontinued.

Furthermore, zetomipzomib or placebo should be interrupted, and the patient should be evaluated if there is a suspected diagnosis of thrombotic microangiopathy, such as with any acute changes in renal function, thrombocytopenia, or intravascular hemolytic anemia.

Patients are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the source document and the eCRF. If a patient withdraws consent, all samples obtained will be retained for analysis unless the patient confirms that he or she wishes the samples to be discarded.

Patients withdrawing from study treatment will complete the ETV (Table 3) followed by the End-of-Study (EOS) visit (Table 3) 4 weeks later to complete the final evaluations according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for patients who complete the study.

8.1.3. Potential Drug-induced Liver Injury

Possible drug-induced liver injury (DILI) will be evaluated throughout the study according to the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (2009). Note that it may be difficult to distinguish DILI from signs of active AIH, and every effort should be made to do so. Patients with significant rises in enzymes consistent with possible hepatocellular injury or cholestatic injury will be considered possible DILI.

Patients meeting the criteria for possible DILI will undergo a pause in IMP administration until a diagnosis can be established. If there is no apparent etiology other than DILI, the patient will be treated according to the treatment guidelines for DILI (Giordano et al., 2014).

8.2. Lost to Follow-Up

The Investigator must make reasonable efforts to contact patients who fail to return for scheduled visits so that they will not be declared "lost to follow-up." Patients will be considered "lost to follow-up" only after reasonable, documented attempts to reach the patient prove unsuccessful. These attempts include, but are not limited to, the following:

1. Attempt contact at all telephone numbers for the patient and his/her listed contacts (to be collected in the source documents at the patient's entry into the study), as applicable.
2. Contact the patient's primary care physician, referring specialist, or other healthcare professional, as applicable.

3. Send emails and texts, and certified letters through the postal service to all the patient's addresses and contacts, as applicable.
4. Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures that may indicate the status of the patient, as applicable.
5. Perform an internet search for additional contact information, as applicable.
6. Check local, regional, and national public records to locate the patient or search for mortality status as allowed by law, as applicable.

The information and dates of attempted contact must be recorded in the patient's records and the patient's final status recorded in the appropriate eCRF. Once all attempts to contact the patient have been exhausted and documented, the Sponsor or Sponsor's designee should be contacted for additional guidance.

9. ADVERSE EVENTS

9.1. Adverse Event Reporting

9.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a clinical study patient administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the IMP. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Hypersensitivity reactions are not anticipated given the structure and mechanism of action of zetomipzomib, but potential hypersensitivity to an excipient could occur. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs will be elicited by asking the patient a nonleading question such as, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” AEs should be reported on the appropriate page of the eCRF.

9.1.2. Assessment of Severity

Severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 5.0). If there is a change in severity of an AE, it must be recorded as a separate event.

9.1.3. Assessment of Causality

AEs will be deemed related to IMP unless clearly unrelated to IMP.

The Investigator will assess the causal relationship between IMP and the AE. One of the categories in Table 5 should be selected based on medical judgment, considering the definitions and all contributing factors.

Table 5: Causality Categories

Related	A clinical event, including laboratory test abnormality, that occurs in a plausible time relationship to treatment administration, and that concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure, if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship to treatment administration. May have negative dechallenge[a] and rechallenge[b] information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

Abbreviations: AE=adverse event

a Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (eg, bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

b Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge).

9.1.4. Action Taken with Regard to Investigational Medicinal Product

The Investigator will describe the action taken with IMP in the appropriate section of the eCRF, as follows:

- None
- IMP stopped
- IMP temporarily interrupted
- IMP dose reduced (with written confirmation from Medical Monitor)
- Other (specify)

9.1.5. Follow-up of Adverse Events

Adverse events are intended to be collected according to the procedures outlined above from the time of informed consent and continuing for 30 days following the last dose, or the EOS Visit, whichever occurs later.

All Investigators should follow up with patient AEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

9.1.6. Documentation and Reporting of Adverse Events

AEs (including SAEs) should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE.

- Diagnosis, or description of the symptoms if a diagnosis is not established (see Section 9.6.1 for specific instructions considered related to IMP tolerability)
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken with regard to IMP
- Outcome of the event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

9.2. Serious Adverse Events

9.2.1. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence or affect that, at any dose:

- Results in death
- Is life-threatening (An AE is life-threatening if the patient was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form.)
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are considered SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF.)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.)
- Results in a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.2.2. Serious Adverse Event Reporting and Documentation Requirements

An SAE must be reported (see Section 9.1.6) by the Investigator if it occurs from the time of signed consent through 30 days after the last dose of IMP, whether or not the SAE is considered to be related to IMP. After the reporting period, SAEs should be reported if the Investigator

assesses the event to be related to IMP. An SAE report consists of the SAE form, provided separately, along with requested additional source documentation as considered necessary.

SAEs that occur during the reporting period must be reported by the Investigator to the Safety Reporting email address [redacted] or dedicated fax number [redacted] on the Study Personnel page and entered into the EDC system within 24 hours from the time the Investigator becomes aware of the SAE. A copy of the SAE form should also be emailed or faxed within 24 hours for the attention of the study safety lead (see Study Personnel page).

The Investigator should not wait for additional information to fully document the event before notification of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained. Follow-up information should be submitted in the same manner as the original SAE report.

Instances of death, congenital abnormality, or an event of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of IMP administration and considered by the Investigator to be related to participation in this study, should be reported to the Medical Monitor.

The Sponsor and/or designee will promptly notify all relevant Investigators and the regulatory authorities of findings that could adversely affect the safety of patients, impact the conduct of the study, or alter the IDMC/Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion of the study. In addition, the Sponsor or designee will expedite the reporting of all adverse reactions that are both serious and unexpected to all concerned Investigators, to the IDMC/IRBs/IECs where required, and to relevant regulatory authorities.

For SAEs that have been reported in the zetomipzomib development program, please refer to the most current zetomipzomib (KZR-616) Investigator's Brochure.

9.3. Pregnancy Reporting

Pregnancy occurring in female patients or female partners of male patients participating in the study or during a clinical investigation must be reported to [redacted] (email address: [redacted]; dedicated fax number: [redacted]) via the Pregnancy Report Form (see Study Personnel page) within 24 hours and entered into the EDC. The outcome of a pregnancy should be followed up carefully, and any abnormal outcome for the mother or the child should be reported. Infants should be followed for a minimum of 8 weeks, and all findings should be reported to the Sponsor. IMP is to be discontinued immediately upon Investigator knowledge of the pregnancy in a female patient.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE (ie, spontaneous abortion [for which any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for expedited reporting of SAEs as outlined in Section 9.2.2.

Any SAE experienced by a patient during pregnancy must be reported as an SAE.

Full details will be recorded on the withdrawal page of the eCRF, or an SAE report will be completed if the patient has completed the study.

9.4. New or Worsening Disease Manifestations

New or worsening manifestation(s) of AIH should not be recorded as AEs unless they are assessed as serious.

9.5. Injection Site Reactions

In study participants who have received zetomipzomib SC, ISRs, including bruising, discoloration, discomfort, erythema, induration, pain, pruritus and/or swelling, have been described in the majority of participants in zetomipzomib studies to date; these events have been transient and predominantly mild. No interventions have been formally studied to prevent or treat these reactions; however, local therapy such as topical antihistamines or glucocorticoids may be helpful, and/or systemic antihistamines, anti-inflammatory drugs, and/or glucocorticoids may be appropriate in more severe cases. The Medical Monitor should be consulted prior to use of glucocorticoids. Investigators should grade and report ISRs. If a patient develops a CTCAE Grade ≥3 ISR, or if a Grade 2 ISR worsens, IMP will be discontinued.

9.6. Adverse Events of Special Interest

An AE of special interest (AESI) is one that is of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a product or compound. Systemic injection reactions and thrombotic microangiopathy have been identified as AESIs, and should be closely monitored and reported within 24 hours using the AE eCRF.

9.6.1. Systemic Injection Reactions

In clinical studies of zetomipzomib, systemic injection reactions associated with SC injections have been reported as TEAEs, consisting of one or more of the following symptoms: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills. The events are associated with an acute phase-like response, including leukocytosis and elevated C-reactive protein, occur approximately 8 to 24 hours after dosing, and usually resolve within 48 hours of dosing. While most commonly associated with an initial dose of zetomipzomib at 60 mg SC and reduced in frequency when initially dosed with 30 mg SC, any or all of these events could occur with lower doses of zetomipzomib or with subsequent higher doses of zetomipzomib. The events are similar to those described for infusion-related reactions observed with the currently approved proteasome inhibitor carfilzomib, which generally occur in the first cycle of dosing.

In reporting TEAEs related to zetomipzomib tolerability, terms such as the NCI-CTCAE terms of ‘infusion-related reaction,’ ‘cytokine release syndrome,’ ‘acute infusion reaction,’ or ‘allergic or hypersensitivity reaction’ should not be used. Instead, each sign or symptom should be recorded as an individual TEAE. If multiple signs or symptoms occur with a given systemic injection-related event, each sign or symptom should be recorded separately with its own level of severity.

Management of these symptoms is described in Section 6.1.2.

9.6.2. Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombocytopenic purpura and hemolytic uremic syndrome, have been described with the proteasome inhibitors, bortezomib, carfilzomib, and ixazomib. The clinical presentation of thrombotic microangiopathy typically includes fever, microangiopathic hemolytic anemia (with schistocytes on blood smear), thrombocytopenia, renal failure, purpura, and neurological manifestations. Patients should be monitored for signs and symptoms of thrombocytopenic purpura/hemolytic uremic syndrome. If the diagnosis is suspected, interrupt treatment with IMP and evaluate. Missed doses should be addressed as per Section 6.1.3.2. If the diagnosis of thrombocytopenic purpura/hemolytic uremic syndrome is excluded, IMP may be resumed. If the diagnosis is confirmed, IMP must be permanently discontinued.

9.7. Unexpected Adverse Reactions

9.7.1. Definition of an Unexpected Adverse Reaction

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of IMP at any dose that is not consistent with the applicable product information (eg, the Reference Safety information of the zetomipzomib [KZR-616] Investigator's Brochure).

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting. The Sponsor or designee shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IRB/IEC within 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IRB/IEC within 15 days after knowledge by the Sponsor of such a case. All Investigators should follow up SUSARs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the patient has completed the clinical study must be reported by the Investigator to the Sponsor.

9.8. Hypersensitivity Reactions

Hypersensitivity reactions are exaggerated or inappropriate immunologic responses occurring in response to an antigen or allergen. Drugs may cause allergic reactions by any mechanism of hypersensitivity. For example, penicillin may cause anaphylaxis, which is IgE-mediated, but most responses are trivial. Hypersensitivity reactions to zetomipzomib are not anticipated given its structure and mechanism of action; however, potential hypersensitivity to an excipient could occur. Studies in compound ONX 0914, an analog of zetomipzomib, demonstrated inhibition of T-helper 2 cell response and allergic reactions in foreign ovalbumin- and house dust mite-induced allergic airway inflammation in mouse models.

Known risk factors for developing a hypersensitivity reaction include allergic reaction history, concomitant diseases such as chronic respiratory diseases, cardiovascular diseases, mastocytosis or clonal mast cell disorders, and severe atopic disease. Some concurrent medications such as beta-adrenergic blockers and angiotensin-converting enzyme inhibitors might also increase the risk. Patients in Study KZR-616-208 should be closely monitored. Should any signs and symptoms of suspected hypersensitivity reactions occur, the Investigator will diagnose per

clinical guideline. Anaphylaxis will be defined and managed using the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria (Sampson et al., 2006), which are outlined in the zetomipzomib Investigator's Brochure. IMP may be temporarily withheld. If the diagnosis of hypersensitivity is confirmed, IMP must be permanently discontinued, and the patient will be treated per guidelines.

9.9. Infections

The usual clinical care for patients with AIH who use chronic immunosuppressives includes surveillance for severe or opportunistic infections, given the increased incidence in this setting. Patients with recent serious or ongoing infections are excluded from the study (Section 4.3). While zetomipzomib has not been associated with new onset or more severe infections to date in patients with similar risk factors, patients will be monitored for new infections, and potential infections (bacterial, viral, or fungal) will be fully evaluated. The periodic physical examination assessments in this study include capturing new onset signs and symptoms. Patients should be encouraged to contact the Investigator if they develop any new signs or symptoms between physical assessments. Clinical care will be provided for any newly diagnosed infection. Patients who use chronic prophylactic or suppressive therapy (eg, chronic antivirals for herpes simplex virus) as part of their usual care are permitted to continue with their usual therapies. Infections will be captured as AEs. In addition to inclusion in the safety data base, the data on infections will be analyzed as part of the glucocorticoid toxicity index (GTI) (Section 7.2.2.4).

9.10. Adrenal Insufficiency

Adrenal insufficiency may be caused by autoimmune diseases such as AIH or by a reduction or discontinuation of exogenous glucocorticoids. The most common symptoms are fatigue, muscle weakness, loss of appetite, weight loss, and abdominal pain. Patients will be educated to recognize the symptoms of adrenal insufficiency. When such symptoms occur, the patient should seek immediate medical care.

9.11. Independent Data Monitoring Committee

The IDMC will convene for safety data review meetings after clinical data are available from the Double-blind Treatment Period Week 12 visit for 6, 12, 18, and 24 patients. After all patients have completed at least 12 weeks of treatment or have withdrawn early, the IDMC will continue to review safety data every 3 to 6 months until the last patient completes the study. Records for AEs, laboratory values (especially ALT), and vital signs will be reviewed. The IDMC may recommend the trial be terminated if major safety concerns related to zetomipzomib are found.

IDMC meetings will be held at mutually agreeable dates and times between the Sponsor and the IDMC members. The Sponsor and the IDMC Chairperson will coordinate the agenda with advance notice to attendees. Meetings may be convened as conference calls or in person. The Sponsor, in consultation with the IDMC Chairperson, may request additional ad hoc meetings of the IDMC with a full quorum should questions of patient safety arise between scheduled meetings. The specific responsibilities and composition will be outlined in a separate IDMC Charter.

10. STATISTICAL ANALYSES

10.1. Overview

Key elements of the statistical analyses for this study are described in this section; details will be documented in a statistical analysis plan (SAP). The statistical analyses for this study will be the responsibility of the Biostatistics department of the Sponsor or [redacted].

The first treatment period of this study will be conducted as a double-blind, randomized study with blinding procedures. For the purpose of the final data analysis, the official, final database will be locked after medical/scientific review has been conducted, protocol deviations have been identified, the data have been declared final and complete, and an SAP has been written and approved. The randomization schedule will be generated and implemented by the external vendor of the study interactive response technology.

No interim analyses are planned for this study. The first planned unblinded analysis of the data will be conducted after all patients have or would have completed the Week 24 visit or EOS visit, whichever occurs later, in the Double-blind Treatment Period, data being fully cleaned and database being "soft" locked to limit changes. The final data analysis will be conducted after all patients have completed the study (Double-blind Treatment Period and OLE Period).

Data will be summarized for all patients as well as the following groups of patients based on treatment received in the Double-blind Treatment Period:

- Group 1: Patients receiving zetomipzomib in the Double-blind Treatment Period and continuing with zetomipzomib in the OLE Period
- Group 2: Patients receiving placebo in the Double-blind Treatment Period followed by zetomipzomib in the OLE Period

10.2. Study Population Definitions

Full Analysis Set (FAS): The FAS is defined as all randomized patients who receive at least 1 dose of IMP or glucocorticoid in this study and have baseline and at least one post-treatment data for the following measures: ALT, AST, IgG, Ishak score, and autoantibodies. For variables with post-baseline missing data, analyses will be carried out using the missing data handling method (to be outlined in the SAP). All observed data will be included in the statistical summaries.

Per Protocol (PP): A PP population may be used to analyze select efficacy endpoints and will be based on zetomipzomib exposure (time on treatment) and protocol deviations.

Safety Population: The safety population will include all randomized patients who received at least one dose of IMP and will be the population used for the analysis of safety data. Adverse event data will be coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA).

10.3. Sample Size and Power Considerations

The statistical analyses of the study data will be descriptive in nature, and no formal hypothesis testing will be performed. No formal statistical sample size or power estimation has been performed.

The sample size of approximately 24 patients was set to allow a preliminary assessment of the potential effect of zetomipzomib with a glucocorticoid, and glucocorticoid treatment with placebo, in patients diagnosed with AIH. This is a signal-seeking study designed to collect data and perform preliminary assessments on safety and efficacy endpoints between treatment groups.

10.4. Background and Demographic Characteristics

Age, height, weight, and other continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum), while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data, including prior medications and coding methodology, will be summarized using frequency tabulations by MedDRA system organ class and preferred term.

10.5. Patient Disposition

Patient disposition (analysis population allocation, screened, randomized, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of patients enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

The statistical analyses of the study data will be descriptive in nature, and no formal hypothesis testing will be performed. No formal statistical sample size estimation has been performed.

Descriptive statistics for continuous variables will be summarized (n, mean, SD, median, interquartile range, minimum, and maximum). Summaries will be presented for the change from Baseline, when appropriate. Categorical variables will be summarized using number of observations (n), frequency and percentages of patients. All percentages will be based on the number of patients in the population unless specified otherwise.

For time-to-event variables (eg, time to CR, time to PR, and time to flare), the Kaplan-Meier method will be used.

Continuous efficacy endpoints (ie, change or percentage change from Baseline in ALT, AST, IgG by visit) will be analyzed using the longitudinal data analysis method based on a mixed model for repeated measures (MMRM) approach. Continuous endpoints will be assessed for normality and log-transformed values may be used if data is not normally distributed. This model will include fixed effect terms for randomized treatment, timepoint (ie, visit) and randomized treatment by timepoint interaction. Within subject error will be modelled by use of an unstructured variance-covariance matrix. Baseline value will be included as a covariate and the randomization stratification factors will be included as class terms.

The Baseline value for ALT, AST, and IgG is defined as the mean of all collected Screening and Day 1 (pre-dose) values. When only one ALT, AST, or IgG result from the Screening visit is

available, that single value will be used for the Baseline. Unless specified otherwise, the baseline value for other parameters, including laboratory data, is defined as the last value prior to the first dose of zetomipzomib or placebo.

All analyses will be performed in SAS® v9.4 for Microsoft® Windows®.

Further details of the statistical methodology, including methods for handling missing data and early withdrawals, will be provided in the SAP that will be finalized prior to any planned unblinded analysis.

10.6.1. Statistical Methods

The statistical analyses of the study data will be descriptive in nature, and no formal hypothesis testing will be performed. No formal statistical sample size estimation has been performed.

Patient baseline characteristics, and the primary and secondary endpoints (Section 2.2), including efficacy, PK, and safety measures, will be summarized using descriptive statistics. A between-treatment difference value in an efficacy endpoint (primary or secondary) will be summarized using a point estimate and a two-sided 95% CI. Statistical uncertainty regarding the efficacy outcome estimate will be presented in a two-sided 95% CI. Change scores from Baseline to follow-up visits (ie, Weeks 12, 14, 16, 24, or OLE visits) on the continuous secondary outcome parameters may be analyzed using the Wilcoxon signed rank test or by log-transformations if data is not normally distributed. Two-sided p-values may be calculated to help assess strength of evidence.

Binary endpoints may be analyzed by the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factor (ie, glucocorticoid use at Screening, no glucocorticoid use at Screening). Patients who have insufficient data for response determination for a time point will be considered non-responders for that time point.

A longitudinal data analysis (LDA) model (Liu et al., 2009; Liang and Zeger, 2000) may be used to analyze continuous endpoints. This model assumes a common mean across treatment groups at Baseline and a different mean for each treatment group at each of the post-Baseline time points. In this model, the response vector consists of the Baseline and post-Baseline values. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The model will also adjust for randomization stratification factors (ie, glucocorticoid use at Screening, no glucocorticoid use at Screening). The continuous endpoints may be log-transformed if they are not normally distributed.

Time to event data (eg, time to CR or PR) will be summarized using the Kaplan-Meier approach.

10.6.2. Multiplicity

Due to the explorative nature of this study, no adjustments will be applied to perform multiple comparisons.

10.6.3. Sensitivity Analysis

Sensitivity analyses will be performed to support the primary analysis of the primary and key secondary endpoints. These analyses use missing data handling methods, where appropriate,

including multiple imputation (Rubin, 1988), all observed data, and tipping point analysis (Yan et al., 2009; Yuan, 2011; Campbell et al., 2011).

10.7. Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including TEAEs, laboratory tests, vital signs, weight, and ECGs. No inferential testing for statistical significance will be performed.

TEAEs will be classified using the MedDRA classification system (Version 25.0 or later). All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IMP. TEAEs leading to death or to discontinuation from treatment and serious TEAEs will also be tabulated. In the by-patient analysis, patients having the same event more than once will be counted only once and by greatest severity.

Summary measure(s) of TEAEs (eg, cumulative incidence rate, exposure-adjusted incidence rate) will be provided. Risk difference in events of interest (eg, AESIs), along with point estimate and 95% CI may be calculated.

Laboratory, vital signs, weight, and ECG data will be summarized descriptively by time point. In addition, shift tables showing the number of patients with low, normal, and high values compared to the normal ranges at Baseline versus post-Baseline will be provided for laboratory tests.

10.8. Interim Analysis

No interim analyses are planned for this study. Periodic evaluations of safety data will be performed throughout this study by the IDMC.

10.9. Other Topics

10.9.1. Biomarker Analysis

Gene transcriptional and proteomic changes following IMP treatment will be assessed. Biomarker profiles of patients in the Active Treatment group and the Control group will be compared. Correlation of clinical outcome and Baseline biomarker profile and longitudinal changes after treatment will also be assessed.

10.9.2. Pharmacokinetic Analysis

Descriptive statistics will be provided for PK assessments of zetomipzomib and its metabolite KZR-59587, and the results will be presented in tabular and graphic form as appropriate.

10.9.3. Subgroup Analyses

Subgroup analyses of key efficacy endpoints by category of the randomization stratification factors, baseline demographic, and disease characteristics will be provided to explore the consistency of the treatment effect across various subgroups and specified in the SAP.

11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

11.1. Compliance Statement

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, ICH guidelines for current Good Clinical Practice (GCP), and the applicable national and local laws and regulatory requirements.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/regional/national requirements, for review and approval before the beginning of the study. On completion of the study conduct, the regulatory authorities will be notified that the study has ended.

11.2. Institutional Review Board or Independent Ethics Committee

Prior to initiation of the study at each study center, the protocol, ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval of the study and all relevant study information must be obtained before the study center can be initiated, and before IMP can be released to the Investigator. Any necessary extensions or renewals of IRB/IEC approval must be obtained for changes to the study (ie, amendments to the protocol, the ICF, or other study documentation). The written approval of the IRB/IEC, together with the approved ICF must be documented in the study files.

The Investigator will promptly report any new information that may adversely affect the safety of the patients or the conduct of the study to the IRB/IEC. The Investigator will submit written summaries of the study status to the IRB/IEC as required, and will inform them when the study has ended.

11.3. Informed Consent and Human Patient Protection

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to current GCP. Patients will provide written informed consent before any study-related procedures are performed. The Investigator is responsible for ensuring that no patient undergoes any study-related examination or activity before that patient has given written informed consent to participate in the study.

The Investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The patient should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the patient will be given ample time to consider the study. Patients will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file. A signed and dated copy of the patient ICF will be provided to the patient.

It should be emphasized that the patient may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the patient's willingness to continue participation in the study, a new ICF will be approved by the IRB(s)/IEC(s) (and regulatory authorities, if required). The study patients will be informed about this new information and consent will be re-obtained.

11.4. Direct Access to Source Data, Source Documents, and Study Reports

The Sponsor or its representatives may periodically check a sample of patient data recorded against source documents at the site. The study may be audited by the Sponsor, designee, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The Investigator will keep records of all original source data. This may include laboratory tests, medical records, and clinical notes. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable review boards with direct access to the original source documents.

The Sponsor or its designee is responsible for preparing a clinical study report. Study results will be provided to the Investigator.

11.5. Data Collection and Handling

An EDC system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the EDC system. Data systems used for the study will have controls and requirements in accordance with local data protection law. The purpose and use of patient personal information collected will be provided in a written document to the patient by the Sponsor or designee.

The remaining biological sample material will be stored off-site at [redacted] and will be accessible to only the Sponsor for up to 2 years after the completion of the study, or until the sample material is entirely used up.

11.6. Confidentiality

Monitors, auditors, other authorized agents of the Sponsor and/or its designee, the IRB(s)/IEC(s) approving this study, the US FDA, and any other applicable agency(ies) will be granted direct access to the patients' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patients, to the extent permitted by the law and regulations.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act and national, regional and/or local laws and regulations on personal data protection.

11.7. Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the Sponsor and designee.

11.8. Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.9. Monitoring

Data for each patient will be recorded on an eCRF. Data collection must be completed for each patient who signs an ICF. The Monitor will carry out source document verification in accordance with current GCP and ICH guidelines at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The Investigator must permit the Monitor, the IRB/IEC, the Sponsor's internal auditors, and representatives from regulatory authorities, direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

Details for monitoring will be provided in a Clinical Monitoring Plan.

11.10. Quality Control and Quality Assurance

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative(s) for compliance with applicable government regulations with respect to current GCP and SOPs.

11.11. Data Management and Coding

The Sponsor or designee will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of Sponsor or designee.

Study centers will enter data into the EDC system by completing the eCRF via a secure internet connection. Data transcribed into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified, and the eCRF will be considered the source document (eSource concept). Any changes to the data entered into the EDC system will be recorded in the audit trail and will be compliant with FDA Code of Federal Regulations (CFR) 21 Part 11.

An essential element of the eSource concept is that the clinical assessment data and other source data is entered during the clinical visit in an eSource EDC system. When designing the system there are some fundamental aspects to be respected:

- The ability of the physician to record clinical information in the patient medical record should not be limited or constrained
- Information should be recorded in line with the current practice at the site
- The integrity of the medical records should not be compromised
- The Sponsor should have access only to pseudonymized information mandated by the protocol

This guidance does not include direct data input from tablets, mobile phones, or other electronic devices.

Medical coding will use MedDRA for concomitant diseases and AEs, and will use the World Health Organization (WHO) drug classifications for medications.

Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

11.12. Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study conduct (ie, following the last patient's last visit), all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years after the discontinuation of clinical development of zetomipzomib. It is the Sponsor's responsibility to inform the study center when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any study-related documentation. In addition, all patient medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor follows local regulatory requirements related to clinical trial registration and results disclosure. Within the United States, the Sponsor complies with the requirements of the Food and Drug Administration Amendments Act of 2007 to register and post results of applicable clinical trials in a timely manner.

The Sponsor is committed to submit for publication in peer-reviewed scientific literature, the results of registered clinical trials involving the Sponsor's products. The Sponsor reserves the right to determine if the results of a registered trial will be submitted for publication and may post the results for registered trials on a clinical trials websites such as www.clinicaltrials.gov or www.clinicaltrialsregister.eu/ as a substitute for a peer-reviewed publication.

The Sponsor often works with clinical trial investigators to produce high-quality manuscripts for publication in various formats including but not limited to abstracts, posters, or presentations. The final clinical study report is intended to form the basis for a manuscript intended for publication in a peer-reviewed scientific journal. The authorship, timetable, and any arrangements for review by the participating investigators will be coordinated by the Sponsor. No partial subset of data from individual investigational sites can be presented or published until after the primary manuscript for the entire study has been accepted for publication in a peer-reviewed scientific journal, with Sponsor consent.

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13. APPENDICES

13.1. Appendix A: Protocol History

Protocol Version	Date Issued	Rationale for Update
Original Protocol, Version 1.0	22 July 2022	N/A
Version 2.0	15 September 2022	[redacted]
Version 3.0	07 March 2023	Added an open-label extension (OLE) treatment period, added options for background medications, and made additional corrections and clarifications.
Version 4.0	26 February 2024	Aligned study efficacy endpoints and associated recommended corticosteroid dose with AASLD AIH guidelines and made additional corrections and clarifications.

13.2. Appendix B: Suggested Glucocorticoid Taper Schedule and Prednisone Equivalents

Table 6 Suggested Glucocorticoid Taper Schedule

Study Week(s)	Prednisone equivalent dose (mg/day) for Both Treatment Groups	Budesonide dose for Both Treatment Groups[a]
0-2	20.0	6 mg/day
3-4	17.5	6 mg/day
5-6	15.0	3 mg/ day
7-8	12.5	3 mg day
9-11	10.0	6 mg/every other day
12-13	7.5	6 mg/every other day
14-24[b]	5.0	3 mg/every other day

[a] Edsbäcker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. C*lin Pharmacokinet* 2004; 43(12): 803-21 (Edsbacker and Andersson, 2004)

[b] After Week 16, the glucocorticoid dose may be tapered further, including discontinuation, at the Investigator's discretion.

Table 7 Prednisone Equivalents

Glucocorticoid	Prednisone Equivalent (mg)
Prednisone	20
Betamethasone	2.4
Cortisone acetate	100
Dexamethasone	3
Hydrocortisone	80
Methylprednisolone	16
Prednisolone	20
Triamcinolone	16

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Approval Task	[redacted] 28-Feb-2024 20:53:19 GMT+0000

Approval Task	[redacted] 28-Feb-2024 23:33:07 GMT+0000

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