



Protocol Title: A Randomized Phase 2 Trial of Atezolizumab and Bevacizumab in Combination With CHS-388 (formerly known as SRF388) or Placebo in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma

Protocol Number: SRF388-201

Phase: 2

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INVESTIGATOR PROTOCOL APPROVAL

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

Institution/Clinic:

Principal Investigator

Printed Name:

Signature:

Date (dd/mm/yyyy):

SPONSOR PROTOCOL APPROVAL

I have read this protocol and approve the design of this trial:

PPD



23-Sep-2024 | 08:54 PDT

Date

Coherus BioSciences, Inc.

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PROTOCOL SYNOPSIS

Trial Title: A Randomized Phase 2 Trial of Atezolizumab and Bevacizumab in Combination With CHS-388 (formerly known as SRF388) or Placebo in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma

Protocol Number: SRF388-201

Phase: 2

Study Drugs:

1. CHS-388/placebo
2. Atezolizumab (Tecentriq®)
3. Bevacizumab (Avastin®)

Trial Population: This trial will enroll approximately 134 patients with first-line advanced or metastatic hepatocellular carcinoma (HCC). Patients will be enrolled in the Lead-In followed by a Randomized Phase:

- Lead-In (n ~ 30)
 - Safety Lead-In: CHS-388 + atezolizumab + bevacizumab (n = 6)
 - Lead-In Expansion: CHS-388 + atezolizumab + bevacizumab (n ~ 24)
- Randomized Phase (n ~ 104)
 - Arm A: CHS-388 + atezolizumab + bevacizumab (n ~ 52)
 - Arm B: placebo + atezolizumab + bevacizumab (n ~ 52)

Trial Duration: Patients will remain on study drug (defined as CHS-388/placebo, atezolizumab, bevacizumab) for up to 2 years or until documented disease progression or unacceptable toxicity. Patients may remain on study drug longer than 2 years with agreement from the trial Investigator and sponsor. The duration of trial participation for a patient is expected to be approximately 4 years, which includes follow-up for survival.

Trial Centers: Enrollment is anticipated at approximately 45 sites in North America and Asia.

Trial Design: SRF388-201 is a Phase 2 trial composed of a Lead-In followed by a Randomized Phase designed to evaluate the efficacy and safety of CHS-388 in combination with atezolizumab plus bevacizumab (Arm A) compared to placebo in combination with atezolizumab plus bevacizumab (Arm B) in patients with first-line advanced or metastatic HCC. After a Safety Lead-In of 6 patients who will receive open-label CHS-388 + atezolizumab + bevacizumab, approximately 24 additional patients will be enrolled in the Lead-In Expansion. The Randomized Phase follows the Lead-In Expansion and will randomize approximately 104 patients with a 1:1 allocation to Arm A or Arm B and stratified by geographic region (Asia excluding Japan vs. rest of world) and Barcelona Clinic Liver Cancer (BCLC) stage (B or C).

Lead-In (Safety Lead-In + Lead-In Expansion)

Safety Lead-In

Six patients will be enrolled in a Safety Lead-In to assess the preliminary safety and tolerability of the triplet combination. Patient dosing will be staggered by 48 hours during the Safety Lead-In, and all patients will receive CHS-388 + atezolizumab + bevacizumab CCI once every 3 weeks (q3 weeks) on Day 1 of a 21-day cycle. CHS-388 CCI mg/kg CCI will be administered first. After an observation period of 30 minutes, the other study drugs may be administered; atezolizumab CCI mg CCI should be administered prior to bevacizumab CCI mg/kg CCI. During the Safety Lead-In, all 6 patients will receive 1 cycle of the triplet combination, during which safety stopping rules will be applied for safety evaluation. If 2 or more of these 6 patients experience a Grade ≥ 3 related adverse event (AE; with the exception of toxicities listed in the table below), any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1, or prolonged delay (defined as > 14-day delay in initiating Cycle 2 due to toxicity), the trial will be halted for safety review with consideration given for evaluating an additional 6 patients at a reduced dose of CHS-388 in conjunction with atezolizumab plus bevacizumab. If < 2 patients experience a Grade ≥ 3 related AE as defined by the safety stopping rules, any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1, or prolonged delay (defined as > 14-day delay in initiating Cycle 2 due to toxicity), then the study will move forward into the Lead-In Expansion. The goal of the safety evaluation for the triplet combination is to evaluate for any signal of unexpected or increased toxicities when given together that would not be observed with any agent alone. As such, a Grade ≥ 3 toxicity known to be associated with any of the 3 study drugs' established safety profiles would not be considered concerning.

Stopping Rule Exceptions for Safety Lead-In

The following Grade ≥ 3 toxicities considered at least possibly related to study treatment would not be considered to meet criteria for a safety stopping rule:	
Nausea	Any Grade ≥ 3 event responding to supportive treatment within 3 days
Vomiting	
Diarrhea	
Fatigue	Grade ≥ 3 lasting < 7 days
Hypertension	Grade ≥ 3 lasting any duration if can be controlled with treatment
Proteinuria	Grade ≥ 3 lasting < 14 days
Asymptomatic amylase/lipase elevations	Grade ≥ 3 lasting any duration if asymptomatic/ no clinical signs of pancreatitis
Thyroid function abnormalities (eg, hypo- or hyperthyroidism)	Grade ≥ 3 lasting any duration if can be controlled with treatment such as thyroid supplementation or beta blockade
Rash	Grade ≥ 3 recovering to Grade 1 with treatment (ie, steroids) within 7 days
Alopecia	Grade ≤ 2 lasting any duration
Non-hematologic laboratory abnormalities	Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, electrolytes, uric acid, etc.

To be considered evaluable for the Safety Lead-In, patients must have completed at least 50% of the prescribed doses of all 3 drugs during the review period (Days 1-21 = Cycle 1) and must not have discontinued treatment during Cycle 1 for reasons other than drug-related AEs. For example, patients who discontinued study treatment during Cycle 1 for progressive disease (PD) or for patient or physician preference but without experiencing a Grade ≥ 3 related toxicity would not be considered fully evaluable for the Safety Lead-In and would be replaced. A 'related' toxicity is defined as those toxicities assessed by the Investigator to be possibly, probably, or definitely related to any study drug.

This analysis set will be used to assess the preliminary safety of the triplet therapy.

Lead-In Expansion

Once the Safety Lead-In of the triplet therapy has met criteria to move forward, the Lead-In will be expanded to enroll approximately 24 additional patients to further assess safety and preliminary efficacy. All patients will receive CHS-388 + atezolizumab + bevacizumab **CC1** once every 3 weeks (q3 weeks) on Day 1 of a 21-day cycle. CHS-388 **CC1** mg/kg **CC1** will be administered first. After an observation period of 30 minutes, the other study drugs may be administered; atezolizumab **CC1** mg **CC1** should be administered prior to bevacizumab **CC1** mg/kg **CC1**.

Safety Review Committee:

The Lead-In (Safety Lead-In and Lead-In Expansion) portion of this study will utilize a Safety Review Committee (SRC), which will meet regularly to review all accumulated data, including safety, PK, pharmacodynamics when appropriate, and preliminary efficacy. The SRC will be composed of a medical representative from the Sponsor, a Medical/Safety Monitor from the Contract Research Organization supporting the trial (if applicable), and all Principal Investigators (or their specified delegates) at each of the enrolling sites. Furthermore, the SRC will be responsible for periodic safety review throughout the treatment period for the Lead-In (Safety Lead-In and Lead-In Expansion), including an assessment of toxicities once all enrolled patients in the Safety Lead-In have completed 1 cycle of treatment. The SRC may recommend pausing enrollment, discontinuing, or expanding any portion of the Lead-In at any time based on a comprehensive review of all clinical data.

Randomized Phase

Trial SRF388-201 will randomize approximately 104 patients to evaluate efficacy and safety of the study drug combination. Patients randomized to Arm A (CHS-388 + atezolizumab + bevacizumab) and Arm B (placebo + atezolizumab + bevacizumab) will be treated q3 weeks on Day 1 of a 21-day cycle. CHS-388 **CC1** mg/kg **CC1** or placebo **CC1** will be administered first. After an observation period of 30 minutes, the other study drugs may be administered; atezolizumab **CC1** mg **CC1** should be administered prior to bevacizumab **CC1** mg/kg **CC1**. See Section 7 for additional details regarding the order and timing of study drug administration.

Independent Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) will be assembled to periodically review all available safety information. Once the first patients enrolled in the Randomized Phase (~10 patients per arm) have completed 1 cycle of treatment, the IDMC will review the safety data. Trial enrollment will continue without pause during IDMC data review of these first 20 patients as well as during subsequent periodic IDMC safety reviews. The IDMC will also review efficacy data at the planned interim analysis. Based on the review of all available data, the IDMC will recommend one of the following actions for the trial: continue as planned, continue with modifications, or stop early.

The IDMC will also review the interim analysis for futility once approximately 50% of the expected PFS events occur. Periodic IDMC data reviews will continue approximately every 4 to 6 months during study conduct.

The Sponsor will make all final decisions regarding any changes in study conduct, taking into account the IDMC recommendations. Membership and responsibilities of the IDMC will be described in a separate IDMC Charter.

Lead-In and Randomized Phase

Response Assessment: Disease response assessments employing computed tomography (CT) or magnetic resonance imaging (MRI) scans will be performed at Baseline and every 9 weeks thereafter (± 7 days) for the trial duration or until disease progression, patient withdrawal, or initiation of additional anticancer therapy. Additional disease assessments such as focused physical examinations and alpha-fetoprotein (AFP) monitoring will also be performed. Patients will be permitted to continue study drug past progression if the patient is willing, meets criteria (Section 4.6) and the treating Investigator agrees the patient is deriving clinical benefit and is not increasingly symptomatic.

Monitoring of Adverse Events: Patients will be monitored continuously for toxicity while on study treatment. Adverse event severity will be assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher. If a patient has an AE of particular severity or an AE that is considered at least possibly related to study drug (CHS-388/placebo, atezolizumab and/or bevacizumab), then dose modifications will be made according to the guidelines set forth in the trial protocol (Section 7.2 and Section 7.5).

Trial Objectives and Endpoints:

All objectives and endpoints are for both the Lead-In and Randomized Phase unless otherwise specified.

Primary Objectives	Primary Endpoints
Lead-In: To evaluate the safety and tolerability of CHS-388 in combination with atezolizumab + bevacizumab	Lead-In: - Nature, frequency, and severity of AEs per NCI-CTCAE version 5.0 or higher - Timing of AEs

Randomized Phase: To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab as measured by progression-free survival (PFS)	Randomized Phase: PFS, defined as time from randomization to occurrence of progressive disease (PD) or death from any cause (whichever occurs first), as determined by Investigator review according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1)
Secondary Objectives	Secondary Endpoints
Efficacy Objectives	Efficacy Endpoints
- To evaluate preliminary measures of efficacy of CHS-388 in combination with atezolizumab + bevacizumab in the Lead-In - To evaluate additional measures of efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab in the Randomized Phase - To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab according to serum Epstein-Barr virus induced gene 3 (EBI3) levels in the Lead-In - To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab according to serum EBI3 levels in the Randomized Phase	- PFS, defined as time from study drug initiation to occurrence of PD or death from any cause (whichever occurs first), as determined by Investigator review according to RECIST v1.1 (Lead-In only) - PFS, defined as time from study drug initiation (Lead-In) or randomization to occurrence of PD or death from any cause (whichever occurs first), as determined by Investigator review according to HCC modified RECIST (mRECIST) - Objective response rate (ORR) as determined by Investigator review according to: - RECIST v1.1 - HCC mRECIST - Duration of response (DoR), defined as time from initial documented objective response to PD or death from any cause (whichever occurs first), as determined by Investigator review according to: - RECIST v1.1 - HCC mRECIST - Disease control rate (DCR), defined as the proportion of patients who experience best overall response of complete response (CR), partial response (PR), or stable disease (SD) - Time to progression (TTP), defined as time from study drug initiation (Lead-In) or randomization to occurrence of disease progression, as determined by Investigator review according to: - RECIST v1.1 - HCC mRECIST - Overall survival (OS), defined as time from study drug initiation (Lead-In) or randomization to death from any cause

	- Time to response, defined as time from study drug initiation (Lead-In) or randomization to initial documented objective response, as determined by Investigator review according to: - RECIST v1.1 - HCC mRECIST - Time on therapy, defined as time from study drug initiation (Lead-In) or randomization to last treatment - PFS, ORR, TTP, and OS by serum EBI3 concentrations
Safety Objective	Safety Endpoints
To evaluate the safety and tolerability of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab in the Randomized Phase	- Nature, frequency, and severity of AEs per NCI-CTCAE version 5.0 or higher - Timing of AEs
Immunogenicity Objectives	Immunogenicity Endpoints
- To characterize the immunogenicity of CHS-388 and atezolizumab - To explore potential correlations between immunogenicity and efficacy, safety, and pharmacokinetic (PK) outcomes	- Incidence of CHS-388 anti-drug antibodies (ADAs) - Incidence of atezolizumab ADAs - Efficacy, safety, and PK endpoints by ADA status
Pharmacokinetic Objectives	Pharmacokinetic Endpoints
- To characterize the PK profile of CHS-388 when given in combination with atezolizumab + bevacizumab - To explore the potential PK impact from drug interaction	- Serum concentrations of CHS-388 - Serum concentrations of atezolizumab
Exploratory Biomarker Objectives	Exploratory Biomarker Endpoints
- To identify and evaluate potential blood or tissue biomarkers of response, resistance, and/or safety - To evaluate the effects of CHS-388 in combination with atezolizumab + bevacizumab on peripheral blood immune cell subsets and circulating cytokines and chemokines	- Assessment of selected blood-based and tumor tissue biomarkers, which may include cytokines, immune cell population subset enumeration and evaluation, programmed death-ligand 1 (PD-L1) expression, gene and protein expression levels, DNA mutation and copy number variations, and correlation of Baseline levels and changes in these markers with clinical outcomes (eg, PFS, ORR) - Changes in peripheral blood immune cell populations by flow cytometry and gene expression

Inclusion Criteria:

All patients must meet the following criteria for inclusion:

1. Patient is ≥ 18 years of age on day of signing informed consent.
2. Patient has unresectable locally advanced or metastatic HCC with diagnosis confirmed by histology/cytology or clinically by American Association for the Study of Liver Diseases criteria (see [Appendix 1](#)) in cirrhotic patients. Patients without cirrhosis require histological confirmation of diagnosis.
3. Patient has had no prior systemic treatment for unresectable locally advanced or metastatic HCC.
4. Patient has BCLC Stage B (not eligible for transcatheter arterial chemoembolization) or Stage C disease.
5. Patient has Child-Pugh Class A disease.
6. Patient has ≥ 1 measurable lesion per RECIST v1.1. Lesion(s) should be suitable for repeat measurement.

Note: Lesions previously treated with radiation or other forms of locoregional therapy must show radiographic evidence of PD to be designated as a target lesion.

7. Patient has an Eastern Cooperative Oncology Group performance status of 0 or 1.
8. Patient has laboratory values indicative of adequate organ function (see table below).

System/Parameter	Laboratory Value
Hematological	
ANC	$\geq 1500/\mu\text{L}$ ($1.5 \times 10^9/\text{L}$)
ALC	$\geq 500/\mu\text{L}$ ($0.5 \times 10^9/\text{L}$)
Platelets	$\geq 75,000/\mu\text{L}$ ($\geq 75 \times 10^9/\text{L}$) without platelet transfusion
Hemoglobin	$\geq 9.0 \text{ g/dL}^a$
Renal	
Creatinine OR CrCl^b (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times \text{ULN}$ OR $\geq 50 \text{ mL/min}$ for patients with creatinine levels $> 1.5 \times \text{institutional ULN}$
Urinalysis for proteinuria	Proteinuria $< 2+$ (within 7 days prior to initiation of study treatment). If $\geq 2+$ proteinuria at Baseline, patient should undergo a 24-hour urine collection and must demonstrate $< 1 \text{ g}$ of protein in 24 hours.
Hepatic	
Total bilirubin	$\leq 3 \times \text{ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 5 \times \text{ULN}$

ALP	$\leq 5 \times \text{ULN}$
Serum albumin	$\geq 2.8 \text{ g/dL}$ ($\geq 28 \text{ g/L}$)
Coagulation	
INR or PT aPTT	$\leq 2 \times \text{ULN}$ unless patient is receiving anticoagulant therapy. For patients receiving anticoagulant therapy, PT, aPTT, or INR should be within the therapeutic range of anticoagulants.
Endocrine	
Calcium	Ionized calcium $\leq 1.5 \text{ mmol/L}$ or calcium $\leq 12 \text{ mg/dL}$, and corrected serum calcium $< \text{ULN}$
Abbreviations: ALC = absolute lymphocyte count; ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; HCC = hepatocellular carcinoma; INR = international normalized ratio; PT = prothrombin time; ULN = upper limit of normal. ^a Criteria must be met without packed red blood cell transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin ($\geq$ approximately 3 months). ^b CrCl should be calculated using the Cockcroft-Gault formula: $(140 - \text{age} [\text{years}] \times \text{weight} [\text{kg}]) / \text{serum creatinine} (\text{mg/dL}) \times 72$	
9. For women of childbearing potential (WCBP): negative serum β human chorionic gonadotropin pregnancy test within 1 week prior to first dose of study drug (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for ≥ 12 consecutive months without an alternative medical cause). 10. WCBP must be willing to refrain from heterosexual intercourse or use acceptable methods of birth control while they are receiving study drug and for 6 months after the last dose of any study drug. Acceptable methods of birth control are described in Section 6.7.5. WCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, female patients must still undergo pregnancy testing as described in the Schedule of Assessments (Table 1 and Table 2). 11. Male patients must be willing to refrain from heterosexual intercourse with a partner of childbearing potential or a pregnant partner or use acceptable methods of birth control while they are receiving study drug and for 6 months after the last dose of any study drug to avoid exposing the embryo. Acceptable methods of birth control are described in Section 6.7.5. Men must refrain from donating sperm during this same period. Azoospermic male patients are exempt from contraceptive requirements. 12. Patient has the ability to adhere to the trial visit schedule and all protocol requirements. 13. Patient has provided signed and dated institutional review board/independent ethics committee-approved informed consent form before any Screening procedures are performed.	

Exclusion Criteria:

Patients are to be excluded from the trial if they meet any of the following criteria:

1. Patient is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
2. Patient has previously received an anti-interleukin (IL)-27 antibody (Ab) or anti-IL-27-targeted therapy.
3. Patient has received prior systemic therapy for unresectable or metastatic disease.

Note: Prior systemic therapies administered for neoadjuvant, adjuvant, or curative intent (localized disease) are permitted if they were given > 1 year prior to the development of recurrent or metastatic disease.
4. Patient has received prior local, neoadjuvant, or adjuvant anticancer therapy > 1 year ago but has not had resolution of any non-immune-related AEs (irAEs) secondary to prior anticancer therapy to Grade ≤ 1 per NCI-CTCAE version 5.0 or higher and/or complete resolution of any irAEs secondary to prior immune checkpoint inhibitor therapy, with the following exceptions:
 - a. Patients with non-irAEs of alopecia, peripheral neuropathy, stable thyroid dysfunction, Grade ≤ 2 controlled rash, and Grade ≤ 2 electrolyte abnormalities on a stable dose of supplementation are eligible even if these AEs have not resolved to Grade ≤ 1 per NCI-CTCAE version 5.0 or higher.
 - b. Patients with the following clinically stable or clinically nonsignificant irAEs are eligible: controlled thyroid disorders, vitiligo, asymptomatic elevated amylase/lipase, type 1 diabetes on insulin, Grade ≤ 2 controlled rash, and Grade ≤ 2 electrolyte abnormalities on a stable dose of supplementation.
 - c. Patients with other clinically stable or nonsignificant AEs from past therapy may be eligible with permission from the Sponsor.
 - d. Patients who discontinued prior treatment due to a Grade ≥ 3 irAE are excluded even if the event has resolved.
5. Patient has known fibrolamellar HCC histology, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.
6. Patient has moderate or severe ascites.
7. Patient has uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).

Note: Patients with indwelling catheters (eg, PleurX™) are eligible.
8. Patient has a history of or current hepatic encephalopathy.
9. Patient is unable to undergo disease evaluation with a triphasic CT or MRI because of contrast allergy or other contraindication.
10. Patient has imaging findings consistent with $\geq 50\%$ liver occupation by HCC tumors.

11. Patient has untreated or incompletely treated varices with bleeding or high risk for bleeding.

Note: Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone EGD within 6 months of study treatment initiation do not need to repeat the procedure.

12. Patient has a history of Grade 4 allergic or anaphylactic reaction to any monoclonal antibody therapy or any excipient in the study drugs.
13. Patient has undergone a major surgical procedure, other than for diagnosis, within 28 days prior to initiation of study treatment, or anticipates the need for a major surgical procedure during the trial.
14. Patient has not fully recovered from surgical resection or ablation within 4 weeks prior to randomization.
15. Patient has symptomatic or untreated brain metastases or leptomeningeal carcinomatosis.

Note: Patients previously treated for brain metastases must be ≥ 28 days from completion of radiation treatment, with follow-up imaging showing no progression, and have no ongoing steroid requirement.

16. Patient has received a prior allogeneic hematopoietic cell transplant or solid tumor organ transplant.
17. Patient has received prior radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior study treatment initiation.

Note: A 7-day washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to bone lesions.

18. Patient has any ongoing radiation-related toxicity or an ongoing corticosteroid requirement due to radiation.
19. Patient has an active or history of autoimmune disease or immune deficiency, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
- Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
 - Patients with controlled type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
 - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (eg, patients with psoriatic arthritis are excluded) are eligible for the study provided all of the following conditions are met:
 - Rash must cover $< 10\%$ of body surface area.

- Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
 - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
20. Patient has medical conditions requiring chronic steroid therapy (ie, > 10 mg/day of prednisone or its equivalent) or anticipates the need for systemic immunosuppressive medications during treatment with study drug, with the following exceptions:
- a. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.
 - b. Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (eg, 48 hours of corticosteroids for a contrast allergy) are eligible.
 - c. Patients who received corticosteroids for chronic obstructive pulmonary disease or asthma or low-dose corticosteroids for orthostatic hypotension are eligible.
21. Patient has a history of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on Screening chest CT scan.
- Note: A history of radiation pneumonitis in the radiation field (fibrosis) is permitted as long as resolved/asymptomatic.
22. Patient has an uncontrolled infection requiring active antimicrobial treatment.
23. Patient has active tuberculosis.
24. Patient has received a live or live-attenuated vaccine within 4 weeks prior to the first dose of study treatment or anticipates the need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab.
- Note: Administration of killed vaccines and approved COVID-19 vaccines is allowed.
25. Patient has known active infection with HIV.
26. Patient has known infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), except for controlled active HBV or fully treated HCV infection, which are eligible and are defined as follows:
- a. For patients with active HBV, controlled disease is considered HBV DNA < 500 IU/mL during the Screening Period with willingness to continue antiviral treatment during the length of the trial. The patient must be on anti-HBV treatment (per local standard of care; eg, entecavir) for a minimum of 14 days prior to trial entry.
 - b. For patients with HCV, only cured disease or HCV considered fully treated and no longer requiring antiviral therapy for control is permitted.

- c. Patients with co-infection with HCV and HBV, defined as HCV RNA positive and hepatitis B surface antigen (HBsAg) positive, are not eligible; however, patients who are HCV Ab+ and HBV core antibody positive but HBsAg- are not considered to have co-infection and are eligible.

27. Patient has inadequately controlled arterial hypertension (defined as systolic blood pressure [BP] ≥ 150 mmHg and/or diastolic BP ≥ 100 mmHg).

Note: Anti-hypertensive therapy to achieve eligibility criteria is permitted. If one session's BP reading is exclusionary, an average of 3 BP readings across 2 sessions can be used to meet eligibility.

28. Patient has a prior history of hypertensive crisis or hypertensive encephalopathy.

29. Patient has had significant vascular disease (eg, aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment.

30. Patient has had a history of hemoptysis (defined as ≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment.

31. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).

32. Current or recent (within 10 days of first dose of study treatment) use of aspirin (≥ 325 mg/day) or treatment with dipyridamole, ticlopidine, clopidogrel, or cilostazol.

33. Chronic daily treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Note: Occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed.

34. Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purposes.

Note: Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an international normalized ratio $\leq 1.5 \times$ upper limit of normal and activated partial thromboplastin time is within normal limits within 14 days prior to initiation of study treatment. For prophylactic use of anticoagulants or thrombolytic therapies, the approved dose as described by the local label may be used.

35. Patient has had a core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the first dose of bevacizumab.

36. Patient has had a history of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment.

37. Patient has had a history of intestinal obstruction and/or clinical signs or symptoms of GI obstruction including subocclusive disease related to the underlying disease or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months prior to initiation of study treatment.

Note: Patients with signs/symptoms of subocclusive syndrome/intestinal obstruction at time of initial diagnosis may be enrolled if they have received definitive (surgical) treatment for symptom resolution.

38. Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure.
39. Patient has a serious, nonhealing or dehiscing wound, active ulcer, or untreated bone fracture.
40. Patient has metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (≤ 30 mm from the carina) of large volume.
- Note: Patients with vascular invasion of the portal or hepatic veins are eligible.
41. Patient has had a history of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to peptic ulcer disease, diverticulitis, or colitis.
42. Patient has had another malignancy, other than those with negligible risk of death, including but not limited to nonmelanoma skin cancer, low-risk localized or cured prostate cancer, ductal carcinoma in situ, or carcinoma in situ of the cervix, within 2 years prior to Screening.
43. Patient has had a history of significant cardiovascular disease such as stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within 6 months prior to Screening.
44. Patient has known New York Heart Association congestive heart failure Grade $\geq$ II.
45. Patient has another unstable or severely uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the risk to the patient associated with his or her participation in the trial.

Statistical Methodology:

Sample Size Determination:

Trial SRF388-201 will enroll a total of approximately 134 patients; approximately 30 patients in the Lead-In followed by the Randomized Phase enrolling approximately 104 patients in a 1:1 randomization stratified by geographic location (Asia excluding Japan vs. rest of world) and BCLC stage (B or C) to assess a primary endpoint of PFS.

In the sample size calculation, the hazard ratio (HR) was calculated using the Weibull distribution with increasing hazard ($\kappa=1.92$), based on the shape of PFS curves in the literature. Of note, the exponential distribution is a special case of the Weibull distribution in that it has a constant hazard. Utilizing a larger alpha (1-sided alpha at 0.05, instead of a 1-sided alpha at 0.025) and appropriately modeling the HR based on the shape of the PFS curve for these patients, the protocol utilizes increased PFS as the primary endpoint. A clinically meaningful difference in median survival of 2.1 months (6.9 months vs 9 months) and the calculation of HR from a Weibull distribution of $[\text{mPFS}(\text{Control})/\text{mPFS}(\text{Experimental})]^{\kappa} = (6.9/9)^{1.92}$ result in the estimated HR of 0.6. Once approximately half of the planned PFS events (ie, 49 of 97) have occurred, an interim analysis for futility only will be performed. If the $\text{HR} \geq 1$, then the trial will stop for futility.

Efficacy Analyses:

The Intent-to-Treat Analysis Set is defined as all patients as randomized. This analysis set will be the primary analysis set for the efficacy analyses for the Randomized Phase. Those without any post-treatment assessment are included and considered as non-responders in this analysis.

The Response-Evaluable Analysis Set is defined for the Lead-In as all Lead-In patients with measurable disease at baseline who received ≥ 1 dose of all assigned study drugs and had ≥ 1 post-Baseline response assessment or who discontinued the treatment phase due to radiographic or symptomatic disease progression (including death caused by disease progression) within 9 weeks after the first dose of study drug. This analysis set will be the primary analysis set for the efficacy endpoints for the Lead-In.

For the Randomized Phase, the Response-Evaluable Analysis Set is a subset of the Intent-to-Treat Analysis Set defined as all patients with measurable disease at Baseline who received ≥ 1 dose of all assigned study drugs and had ≥ 1 post-Baseline response assessment or who discontinued the treatment phase due to radiographic or symptomatic disease progression (including death caused by disease progression) within 9 weeks after the first dose of study drug. This analysis set will be used as a sensitivity analysis for efficacy endpoints for the Randomized Phase.

Safety Analyses:

The Safety Lead-In Evaluable Analysis Set ($n = 6$) is defined as patients enrolled in the open-label Safety Lead-In, who either experienced a Grade ≥ 3 related AE during the first cycle of therapy (Days 1-21) or who completed at least 50% of the prescribed combination therapy doses. The aggregate safety data of these patients during Cycle 1 will be reviewed by the SRC prior to initiating enrollment in the Lead-In Expansion.

The Lead-In Safety Analysis Set ($n \sim 30$) is defined as the patients enrolled in the open-label Lead-In (Safety Lead-In plus the Lead-In Expansion) who received any amount of study drug (CHS-388, atezolizumab, or bevacizumab). This analysis set will be the primary analysis set for all safety endpoints in the Lead-In.

The Randomized Safety Analysis Set is defined as all patients who received any amount of study drug (CHS-388/placebo, atezolizumab, or bevacizumab) in the Randomized Phase, with treatment group designated per actual study drug received. This analysis set will be the primary analysis set for all safety endpoints in the Randomized Phase.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher and will be graded according to the NCI-CTCAE version 5.0 or higher.

The numbers and types of AEs experienced will be summarized in a by-patient listing. The listing will include the description, severity, and relationship of the events to study drug (CHS-388/placebo, atezolizumab, and/or bevacizumab).

Summaries of AEs will be based on treatment-emergent adverse events (TEAEs). A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment to 30 days after the last dose of study treatment.

TEAEs will be summarized by treatment arm, frequency, and by MedDRA system organ class and preferred term. Separate tabulations will also be produced for TEAEs assessed as related to study drug, TEAEs that led to treatment discontinuation, TEAEs that led to death, AEs of special interest, and TEAEs Grade ≥ 3 in severity. Treatment-emergent serious adverse events (SAEs) and SAEs related to study drug will also be tabulated.

Shifts in grade (per NCI-CTCAE version 5.0 or higher) from Baseline to the maximum post Baseline grade will be summarized.

Table 1: Screening Assessments Checklist

• Informed consent^a • Inclusion/exclusion criteria • Medical history and demographics • Cancer history and disease characterization^b • Prior/concomitant medications and procedures^c • Full physical examination^d • ECOG performance status • ECG (12-lead)^e • Blood chemistry^f • Hematology^f • Fasting lipid panel^f • Coagulation^f • Urinalysis^f	• Hepatitis serology^g • HBV DNA (patients with a history of hepatitis B infection)^g • HCV viral load (patients with a history of hepatitis C infection)^g • HIV^h • Serum βhCG pregnancy testⁱ • Buccal swab for pharmacogenomics^j • Tumor imaging^k • AE/SAE assessment^l • Archival tumor tissue^m • Tumor biopsyⁿ • EGD (if none in last 6 months)^o • AFP • Blood for EBI3 biomarker
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Abbreviations: Ab = antibody; AE = adverse event; AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; β hCG = β human chorionic gonadotropin; C1D1 = Cycle 1 Day 1; CT = computed tomography; EBI3 = Epstein-Barr virus induced gene 3; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EGD = esophagogastroduodenoscopy; EoT = End of Treatment; HBcAb = HBV core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; ICF = informed consent form; mRECIST = modified Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; QTc = QT interval corrected; QTcF = QT interval corrected with Fridericia's method; SAE = serious adverse event; WCBP = women of childbearing potential.

Note: All Screening assessments will be performed ≤ 30 days prior to the first dose of study drug. See Section 6 for details on each study assessment.

- ^a Informed consent must be obtained prior to performing Screening assessments unless otherwise noted (see Section 6.1.1). Standard-of-care assessments performed within 30 days of C1D1 do not need to be repeated.
- ^b Disease characterization including but not limited to Child-Pugh score (see Appendix 3) and BCLC stage (see Appendix 4).
- ^c Includes medications received and medical procedures performed within the previous 30 days (live attenuated vaccines within the previous 42 days) and any cancer treatment procedures from any time in the past (see Section 6.1.4).
- ^d Full physical examination parameters are described in Section 6.1.5.
- ^e A 12-lead ECG will be conducted following an approximately 10-minute rest period. QTc measurements will use QTcF. During Screening, collect 1 individual tracing. If there is 1 elevated QTc reading, the Screening requirement can be met with the average of triplicate ECGs.
- ^f For a list of all blood chemistry, hematology, lipid panel, and coagulation parameters and urinalysis details, see Section 6.1.9. Patients should be fasting prior to collection of the lipid panel.
- ^g All patients will be tested for anti-HCV Ab and HBsAg at Screening. If Ab test is positive, hepatitis C RNA (viral load) or HBV DNA will be collected. Patients with a positive anti-HCV and HCV RNA titer or HBsAg test will be excluded from enrolling in the trial (except for patients with controlled viral disease as outlined in Section 5.2). While patients with HCV and HBV co-infection, defined as HCV RNA positive and HBsAg positive, are not eligible, patients who are HCV Ab+ and HBcAb+ but HBsAg- are not considered to have co-infection and are eligible.
- ^h Patients without documentation of a prior negative HIV test result (eg, Ab, antigen, or polymerase chain reaction-based test) are required to undergo HIV testing during Screening. Only patients with negative HIV results will be eligible to enroll.

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- ⁱ For WCBP, the Screening pregnancy test will be serum and must be performed within 7 days prior to the first dose to confirm eligibility.
- ^j May be collected during Screening or at C1D1 (collection should be completed prior to dosing, see [Table 2](#)).
- ^k Quantification of Baseline disease burden will be done with liver CT or MRI (optimized for pre-contrast, arterial, and portal venous phase [eg, triphasic or other institutional HCC protocol adequate for mRECIST evaluation]) and contrast-enhanced CT or MRI of the chest, abdomen, and pelvis. Other scans may be performed (eg, brain MRI, bone scan) if clinically indicated or if the area is a site of known disease. The modality chosen to evaluate each individual patient should be the same throughout the duration of the study, when possible. See Section 6.3 for more information on the specific disease response assessment to be conducted at Screening.
- ^l AEs/SAEs should be monitored from the time of the signing of the ICF until the patient has been deemed to be a screen failure. After completion of the initial Screening assessments, any new clinically significant findings for enrolled patients will be captured as an AE on the eCRF. SAEs for all patients will be reported from the time of the signing of the ICF. At any time after completion of the AE reporting period, if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to any study drug, the event must be reported.
- ^m Archival tumor tissue with associated pathology report collected within 18 months prior to enrollment is required to be collected, if available. Newly obtained core or excisional biopsy of a tumor lesion not previously irradiated is optional and preferred to archival tissue. Formalin-fixed paraffin embedded tissue blocks are preferred to slides. Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Laboratory Manual).
- ⁿ Screening tumor biopsy is required if no cirrhosis and no prior histological confirmation of HCC diagnosis. All other tumor biopsies are optional unless otherwise specified. Optional tumor biopsies are to be obtained for relevant patients at Screening and again any time after dosing during Cycle 2 or at EoT, whichever comes first. A +7 day window for scheduling is permitted for EoT biopsies. Please see Section 6.1.12 for more details.
- ^o Patients must undergo an EGD, and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone EGD within 6 months of study treatment initiation do not need to repeat the procedure.

Table 2: Schedule of Assessments: CHS-388/Placebo + Atezolizumab + Bevacizumab, q3 week Dosing

	Cycle 1		Cycle 2	≥ Cycle 3	EoT ^a	Safety Follow-Up ^b	Long-Term Follow-Up ^c	Survival Follow-Up ^d
	(21 d ± 2)		(21 d ± 2)	(21 d ± 2)				
Assessments	D1	D8 ± 2	D1	D1	≤ 7 d from treatment termination	30 (+ 5) d from last study drug dose	90 (+ 5) d from last study drug dose	Every 6 months (± 4 weeks)
Concomitant medications and procedures	X	X	X	X	X	X	X	
AE/SAE assessment ^{b,c}	X	X	X	X	X	X	X	
Symptom-directed physical examination ^e	X ^{f,g}	X	X ^g	X ^g	X	X		
ECOG performance status	X ^{f,g}	X	X ^g	X ^g	X	X		
ADA assessment ^h	See Table 3							
Pharmacokinetics ^h								
Urinalysis ⁱ	X		X	X	X	X		
Blood chemistry, hematology, coagulation ^j	X ^{f,k}	X	X ^k	X ^k	X	X		
Thyroid function testing ^l	X ^g			X ^{g,l}				
βhCG pregnancy test ^m	X ^{f,g}		X ^g	X ^g	X	X		
AFP	X ^g		X ^g	X ^g				
HCV viral load ⁿ	X ^f		X	X				
HBV DNA ^o	X ^f		X	X				
Blood for PBMC immunophenotyping ^p	X ^g		X ^g		X			
Blood serum for cytokine analysis ^q	X ^q		X ^q		X			

	Cycle 1		Cycle 2	≥ Cycle 3	EoT ^a	Safety Follow-Up ^b	Long-Term Follow-Up ^c	Survival Follow-Up ^d
	(21 d ± 2)		(21 d ± 2)	(21 d ± 2)				
Assessments	D1	D8 ± 2	D1	D1	≤ 7 d from treatment termination	30 (+ 5) d from last study drug dose	90 (+ 5) d from last study drug dose	Every 6 months (± 4 weeks)
Blood for EBI3 biomarker ^r	X ^g		X ^g	X ^g	X			
Buccal swab for pharmacogenomics ^s	X							
Tumor biopsy ^t			X		X			
CHS-388/Placebo administration ^u	X		X	X				
Atezolizumab administration ^u	X		X	X				
Bevacizumab administration ^u	X		X	X				
Disease response assessments ^v				X ^v	X			
Survival ^d								X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; AFP = alpha-fetoprotein; βhCG = beta human chorionic gonadotropin; C = cycle; D or d = day; EBI3 = Epstein-Barr virus induced gene 3; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PK = pharmacokinetics; q3 weeks = once every 3 week(s); SAE = serious adverse event; T4 = free thyroxine 4; TSH = thyroid stimulating hormone.

Note: Cycle = 21 days.

^a The EoT Visit should occur for any patient who discontinues all study drugs. Each assessment need not be performed if the patient had an identical assessment within the previous 2 weeks or, in the case of disease response assessments, in the previous 30 days.

^b All patients will have a Safety Follow-up Visit approximately 30 (+ 5) days after the last dose of study drug (CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later). AEs are collected through 30 days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later. If possible, this visit should occur prior to the initiation of any subsequent anticancer therapy. At minimum, this visit should include collection of AEs/SAEs and concomitant medications/procedures. This visit can be performed by telephone call if the patient does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinic visit will be required.

- ^c Long-term follow-up assessments continue for up to 90 (+ 5) days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later, to collect SAEs, AESIs, and pregnancy events. Long-term follow-up reporting may be conducted in person or by phone. Any pregnancies and exposure during pregnancy that occur within 90 days after the last dose of any study drug are to be reported by the Investigator.
- ^d All patients will be followed for survival every 6 months for 4 years from randomization. This assessment can be conducted by telephone interview or medical chart review. Information on initiation of other anticancer therapy (including start date, therapy type, and response on treatment) will also be collected.
- ^e The physical examination at C1D1 is symptom-directed only; a full examination is not needed unless indicated. Physical examination will include an evaluation of disease-relevant systems and capture of vital signs. Patient weight should be taken predose on Day 1 of each cycle to calculate the appropriate doses of CHS-388/placebo and bevacizumab to be administered on that cycle. Alternatively, sites may follow their institutional practice of using the C1D1 weight to dose throughout the study unless there is a > 5% change. While D1 physical examinations must be conducted in person or per institutional standards, physical examinations on all other visit days may be done by telemedicine following institutional procedures.
- ^f Screening evaluations performed within 7 days of the first dose (C1D1) can be used, and assessments do not need to be repeated. If a physical examination, ECOG performance status assessment, β hCG pregnancy test, HCV viral load assessment, or HBV DNA assessment was not performed within 7 days of C1D1, it should be completed within 48 hours prior to dosing.
- ^g Assessments/sample collection should be completed within 48 hours prior to dosing.
- ^h An additional blood sample for CHS-388/placebo PK and ADA should be drawn at the time of any unusual safety event (ie, an AE different in type and severity from that which is expected in the setting of CHS-388, atezolizumab, or bevacizumab use).
- ⁱ Collect urine sample prior to each cycle. A urine dipstick or full urinalysis can be performed. Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle as results must be available prior to treatment administration. Patients with Grade 2 proteinuria must undergo a 24-hour urine collection prior to the subsequent bevacizumab CCI. Patients with Grade 3 proteinuria must undergo a 24-hour urine collection prior to the current bevacizumab CCI. Samples do not need to be collected at the EoT or Safety Follow-up visits if the patient had no proteinuria during treatment.
- ^j Coagulation should be assessed at Baseline for all patients. For patients receiving anticoagulation therapy, coagulation should be assessed as needed per the patient's routine monitoring.
- ^k On dosing days, blood chemistry, hematology, and coagulation laboratory samples should be collected within 48 hours prior to dosing. Additional (unscheduled) assessments should be performed as clinically indicated. See Section 6.1.9 for detailed parameters.
- ^l Perform TSH and free T4 tests on C1D1, C4D1, and every 3 cycles thereafter (C7D1, C10D1, C13D1, etc.).
- ^m For women of childbearing potential only. May be either urine or serum and performed every cycle predose while on treatment.
- ⁿ HCV viral load will be assessed in patients who have a history of hepatitis C infection. Serial monitoring should be conducted only in patients who have known disease.
- ^o HBV DNA will be assessed in patients who have a history of hepatitis B infection. Serial monitoring should be conducted only in patients who have known disease.
- ^p PBMC immunophenotyping by flow cytometry analysis will be used for quantitation and relative frequency of various immune cell subsets. PBMC samples are to be collected predose at C1D1 and C2D1, as well as at the EoT visit.
- ^q Blood serum samples for cytokine analysis should be collected at 3 timepoints: (1) predose on C1D1 and C2D1; (2) 6 hours postdose on C1D1 and C2D1; however, if a 6-hour postdose sample is not feasible, the sample may be collected at any point from 4 to 36 hours post dose; and (3) at the EoT visit. Analytes will include but are not limited to cytokines, chemokines, and other soluble factors.
- ^r Blood for EBI3 biomarker should be collected at Screening, Cycle 1, Cycle 2, Cycle 4, every 9 weeks thereafter, and at the EoT visit.
- ^s Collect prior to dosing at C1D1 if not collected at Screening.
- ^t On-therapy tumor biopsies are optional and are to be obtained for relevant patients at any time after dosing during Cycle 2 or at EoT, whichever comes first. A +7-day window for scheduling is permitted for EoT biopsies. Please see Section 6.1.12 for more details.

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- ^u Patients will receive CHS-388/placebo, atezolizumab, and bevacizumab q3 weeks until documented disease progression or unacceptable toxicity through C35. Doses of CHS-388/placebo, atezolizumab, and/or bevacizumab may be administered within a $\pm$ 3-day window. See Section 7 for additional details regarding the order and timing of study drug administration.
- ^v Imaging will be performed every 9 weeks (ie, beginning C4D1 [$\pm$ 7 days] followed by C7D1, C10D1, C13D1, etc.) and should include imaging consistent with anatomic areas and modality used at Screening. Response evaluation by Investigator should be done per response criteria (see Section 6.3.1). These evaluations will be conducted on treatment or following treatment discontinuation until the patient experiences PD, discontinues the study, or initiates additional anticancer therapy. The Sponsor may collect copies of the patient images of all disease-specific assessments obtained on study. For patients who experience an objective response or who progress on therapy and continue treatment past progression, confirmatory scans should be done a minimum of 4 weeks and a maximum of 9 weeks later.

Table 3: Schedule of Pharmacokinetic and Anti-Drug Antibody Assessments: CHS-388/Placebo + Atezolizumab + Bevacizumab, q3 week Dosing

Cycle	Day	Scheduled time point	CHS-388/Placebo PK sample ^a	Atezolizumab PK sample	CHS-388/Placebo ADA sample ^a	Atezolizumab ADA sample
1	1	CCI	X	X	X	X
		Immediately CCI (+ 30 min)	X	X		
2 and 3	1	CCI	X	X	X	X
4	1	CCI	X	X	X	X
		Immediately CCI (+ 30 min)	X			
5 and beyond	1	CCI	X	X ^c	X	X ^c
EoT	--	--	X	X	X	X

Abbreviations: ADA = anti-drug antibody; EoT = End of Treatment; PK = pharmacokinetics; q3 week(s) = once every 3 weeks.

^a An additional blood sample for CHS-388/placebo PK and ADA should be drawn at the time of any unusual safety event (ie, an AE different in type and severity from that which is expected in the setting of CHS-388, atezolizumab, or bevacizumab use).

^b CCI is defined as prior to CCI of all study drugs.

^c After Cycle 4, atezolizumab PK and ADA samples should only be collected on Day 1 of Cycle 8, Cycle 12, and Cycle 16, as well as EoT.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
Ab	antibody
ACTH	adrenocorticotrophic hormone
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AFP	alpha-fetoprotein
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
aPTT	activated partial thromboplastin time
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the concentration versus time curve
AUC ₍₀₋₁₆₈₎	AUC from the start of dose administration to 168 hours postdose
BCLC	Barcelona Clinic Liver Cancer
BP	blood pressure
βhCG	beta human chorionic gonadotropin
C	Cycle
C _{max}	maximum concentration
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
C _{trough}	trough concentration
D/d	Day/day
DCR	disease control rate
DoR	duration of response
EBI3 or IL27B (human) or Ebi3 (mouse)	Epstein-Barr virus induced gene 3
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation	Definition
EGD	esophagogastroduodenoscopy
EoT	end of treatment
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
gp130	glycoprotein 130
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IFN γ	interferon gamma
Ig	immunoglobulin
IL	Interleukin
IL-27RA (WSX-1) (human) or Il-27ra (mouse)	IL-27 receptor subunit alpha
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
IRF	independent review facility
CCI	
IRT	Interactive Response Technology
IV	intravenous(ly)
JAK	Janus kinase

Abbreviation	Definition
LAG3	lymphocyte activating 3
LMWH	low molecular weight heparin
LN	lymph node
MAS	macrophage activation syndrome
MCP-1/CCL2	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MIP-1 α /CCL3	macrophage inflammatory protein-1 alpha
MIP-1 β /CCL4	macrophage inflammatory protein-1 beta
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
CCI	
NASH	non-alcoholic steatohepatitis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
p28 or IL27A	IL-27 subunit alpha
PBMC	peripheral blood mononuclear cell(s)
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death-ligand 1
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
pSTAT	phosphorylated signal transducer and activator of transcription
PT	prothrombin time
q3 weeks	once every 3 weeks
q4 weeks	once every 4 weeks
QTc	QT interval corrected

Abbreviation	Definition
QTcF	QT interval corrected with Fridericia's method
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
rhIL-27	recombinant human IL-27
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SRC	Safety Review Committee
STAT	signal transducer and activator of transcription
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TIGIT	T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibition motif (ITIM) domains
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TNF α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of normal
US	ultrasound
VEGF	vascular endothelial growth factor
WCBP	women of childbearing potential

1. BACKGROUND

1.1. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common form of liver cancer and mainly occurs in the context of cirrhosis, hepatitis B or C virus infection, or non-alcoholic steatohepatitis (NASH). An increased risk for HCC has been reported in African Americans with hepatitis B, Asian males ≥ 40 years, and Asian females ≥ 50 years.¹ The incidence is 3 times higher in males than females.² Due in part to a lack of symptoms in its early stages, HCC is often not diagnosed until it is more advanced.

Globally, HCC was the sixth most commonly diagnosed cancer and the third leading cause of cancer deaths in 2020, resulting in 905,677 new cases and 830,180 deaths.² East Asia had the highest incidence, closely followed by Micronesia, North Africa, Southeast Asia, and Melanesia. In North America, the incidence rate is 6.9 per 100,000; however, in Western Europe, the incidence is 5.6 per 100,000.

Systemic therapy options for advanced-stage patients who have metastatic disease at diagnosis or who have progressed after locoregional treatment generally include vascular endothelial growth factor (VEGF)-targeted therapies and programmed death receptor-1 (PD-1) pathway blockade.^{3,4} Single-agent VEGF receptor tyrosine kinase inhibitor monotherapy such as sorafenib and lenvatinib has been the backbone of first-line therapy until the recent approval of atezolizumab plus bevacizumab in the United States in 2020. In the pivotal IMbrave 150 trial, 501 patients were randomized in a 2:1 fashion to either atezolizumab + bevacizumab or sorafenib.⁵ The combination of atezolizumab and bevacizumab improved overall survival (OS) and independent review facility (IRF)-assessed progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). In an updated analysis that included 12 additional months of follow-up (median 15.6 months), median OS was 19.2 months for atezolizumab plus bevacizumab compared to 13.4 months for sorafenib (hazard ratio [HR] 0.66, 95% CI 0.52-0.85, $p = 0.0009$).⁶ Median PFS per IRF-assessed RECIST v1.1 was 6.9 months with atezolizumab and bevacizumab vs. 4.3 months with sorafenib (HR 0.65, 95% CI: 0.53-0.81, $p=0.0001$) and objective response rates (ORR) were 30% (8% with a complete response [CR]) versus 11% ($< 1\%$ with a CR), respectively.

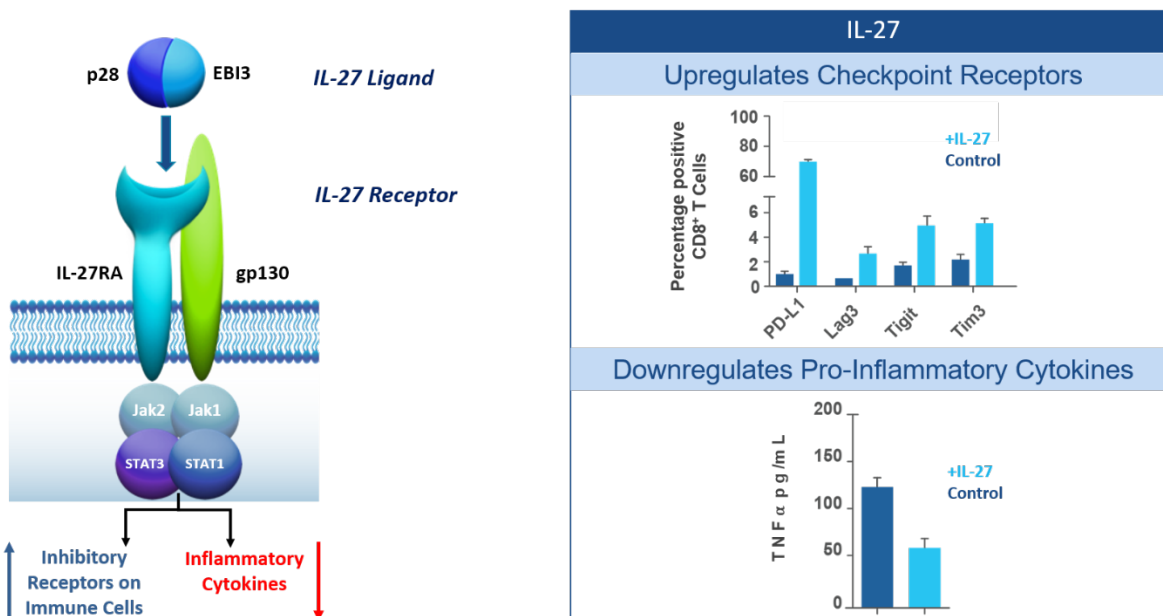
While the combination of atezolizumab and bevacizumab is an important advance in the treatment of first-line metastatic HCC, there remains a large unmet clinical need for the 70% of patients who do not experience an objective response or who progress after 7 months.

1.2. Role of IL-27 in Cancer

Interleukin (IL)-27 is a heterodimeric cytokine of the IL-12/IL-23 family that is composed of 2 subunits, IL27A (also known as p28 or IL-30) and IL27B (also known as Epstein-Barr virus induced gene 3 [EBI3]). These subunits are transcribed and secreted by activated antigen presenting cells such as macrophages and dendritic cells,⁷ but they are also transcribed independently of each other in certain cell types.⁸ IL-27 signals through a heterodimeric receptor composed of IL-27 receptor subunit alpha (IL-27RA [WSX-1]) and glycoprotein 130 (gp130).⁷ While gp130 is expressed by most cell types, IL-27RA (WSX-1) expression is more restricted and found predominantly on cells of hematopoietic origin including T cells, B cells, natural killer

(NK) cells, and monocytes.⁹ Binding of IL-27 to its receptor activates signaling through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway as depicted below in Figure 1.¹⁰ This signaling can alter the expression of immune-regulatory receptors and cytokines in several immune cell populations and plays a role in quelling T cell-mediated inflammation during infection.^{11, 12}

Figure 1: IL-27 results in upregulation of immune checkpoint receptors and decreased production of proinflammatory cytokines



Abbreviations: EBI3 = Epstein-Barr virus induced gene 3; gp130 = glycoprotein 130; IL-27= interleukin 27; IL-27RA = IL-27 receptor subunit alpha; JAK = Janus kinase; LAG3 = lymphocyte activating 3; p28 = IL-27 subunit alpha; PD-L1 = programmed death-ligand 1; STAT = signal transducer and activator of transcription; TIGIT = T cell immunoreceptor with immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibition motif (ITIM) domains; TIM3 = T cell immunoglobulin and mucin-domain containing-3; TNFα = tumor necrosis factor alpha. Source: Chihara et al, 2018; DeLong et al, 2019; Rausch et al, 2019 ¹³⁻¹⁵

There is evolving data to support IL-27's role in cancer etiology. Microarray studies of CD4⁺ T cells identified programmed death-ligand 1 (PD-L1) as a target of IL-27 signaling.¹⁶ IL-27 is also a potent inducer of T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activating 3 (LAG3), and T cell immunoreceptor with immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibition motif (ITIM) domains (TIGIT) on CD4⁺ T cells.^{14, 17} Moreover, mice lacking either EBI3 or IL-27RA demonstrate reduced tumor growth in mouse models of B16 melanoma, and in both of these settings, CD8⁺ T cells are important for mediating the antitumor response.¹⁷⁻¹⁹ In the context of the B16 melanoma model, RNA and protein expression profiling at single cell resolution identified IL-27 as a key driver of gene signatures for multiple states of T-cell dysfunction, including CD8⁺ T cell exhaustion as well as antigen-specific and nonspecific CD4⁺ T cell tolerance.¹⁴ Collectively, these findings suggest that targeting IL-27 may be a promising therapeutic strategy for the treatment of cancer.

1.2.1. Role of IL-27 in HCC

There are several lines of evidence to support the hypothesis of the role of IL-27 in HCC. In animal models of HCC, IL-27RA deficiency leads to decreased tumor growth in mice. In a genetic model of HCC, treatment with an antibody against IL-27, CHS-388, inhibits the development of HCC.²⁰ In a model of established HCC, CHS-388 has substantial, dose-dependent tumor-inhibitory activity and leads to a reduction in the expression of genes associated with tumor burden and immune inhibitory receptors.²⁰

In humans, to explore the role of IL-27 in the development of HCC, Yuan et al²¹ conducted 2 parallel case-control studies using data from the Singapore Chinese Health Study and the Shanghai Cohort Study. Each study included 100 HCC cases and 100 individually matched controls. Human IL-27 protein was quantified in sera that were collected, on average, 4.5 years prior to the diagnosis of HCC. In both studies, serum IL-27 levels were significantly higher in persons who subsequently developed HCC than controls who remained free of HCC. In the Singapore Chinese Health Study, the odds ratio (OR) of developing HCC for the highest IL-27 tertile was 46.08 (95% CI, 4.68-453.86) compared with the lowest tertile; in the Shanghai Cohort study, the corresponding OR was 19.09 (95% CI, 3.81-95.57), both with $P_{\text{trend}} < 0.001$.

Combining both cohorts, for patients who were hepatitis B surface antigen (HBsAg) negative, the OR was 42.47 (95% CI, 8.30-217.40) and for patients who were HBsAg positive, the OR was 242.96 (95% CI, 38.42-1,529.01) compared with patients in the lowest tertile of IL-27 who were HBsAg negative. These studies revealed that elevated levels of IL-27 in prediagnostic sera were significantly closely associated with an increased risk of developing HCC. These findings support the potential contributory role of IL-27 in the development of HCC and its potential use as a predictive biomarker in HCC development.

Additional efforts by Coherus BioSciences, Inc. have evaluated the protein concentrations of the CCI of IL-27 in serum samples from patients with multiple cancer types and healthy donors to understand which tumor types are potentially associated with activation of the IL-27 pathway. CCI (Figure 2), elevated serum CCI concentrations CCI were frequently found in patients with CCI HCC CCI and CCI and statistically significant increases in CCI concentrations were found when comparing serum samples from patients with CCI HCC, CCI with those of healthy donors.

Figure 2:

CCI



CCI

In a second independent cohort of patient samples, CCI concentrations were tested CCI in serum from CCI HCC, CCI

Patients with HCC were grouped into tertiles based on normalized serum concentration of CCI and correlated with OS data (Figure 4). HCC patients with serum CCI

concentrations within the highest tertile had the poorest OS, while those patients within the lowest tertile had the best OS. These data indicate that elevated serum concentrations of the CCI of IL-27 is associated with poor outcome in patients with HCC. These data, combined with the immune inhibitory properties of this cytokine, suggest that blocking IL-27 may increase antitumor immune response in patients with HCC. Additional data from The Cancer Genome Atlas revealed that the IL-27 messenger RNA levels in primary liver cancer was ≥ 20 times higher than that of any other cancer.

Figure 3: CCI

CCI

Figure 4: CCI

CCI

1.3. CHS-388

CHS-388 is a novel fully human anti-IL27 IgG1 monoclonal antibody that targets the IL-27 subunit alpha (p28) by binding to p28 with high affinity, thereby blocking the interaction between IL-27 with its receptor resulting in enhanced immune activation in the tumor microenvironment. Target binding studies showed that CHS-388 has very high affinity for recombinant human IL-27 (rhIL-27), high affinity for recombinant rat and cynomolgus monkey IL-27, and lower affinity for recombinant mouse IL-27. Ligand-receptor blocking studies demonstrated that CHS-388 blocks the interaction of rhIL-27 with rhIL-27 receptor alpha (rhIL-27RA [WSX-1]). Signaling inhibition studies showed that CHS-388 blocks IL-27-mediated phosphorylation of signal transducer and activator of transcription (pSTAT) in a human monocytic cell line, in primary human peripheral blood mononuclear cells (PBMCs), and in lymphocytes from whole blood from different species. In addition, CHS-388 was found to block downstream IL-27-mediated changes in CCI in primary human immune cells. CHS-388 increased CCI production from activated human PBMC cultures in a subset of donors, and when tested with an anti-PD-1 antibody, the combination led to a significantly higher concentration of CCI production (Figure 5 [top]) compared to either antibody treatment alone. Similarly, it blocked IL-27-induced inhibitory receptor expression by immune cells (CCI shown in Figure 5 [bottom]). Increased CCI production was not observed in resting PBMC cultures treated with either CHS-388, anti-PD-1, or the combination of both antibodies. In vivo, CHS-388 blocked murine IL-27 signaling and demonstrated antitumor activity in mouse models of HCC and lung metastases; bound to and blocked the

signaling activity of human IL-27 overexpressed in mice; and led to a time-dependent accumulation of p28 in the plasma of mice.

Figure 5: CCI

CCI

1.3.1. Summary of Nonclinical Safety of CHS-388

The nonclinical toxicology program conducted in support of clinical trials with CHS-388 consisted of a single-dose CCI pharmacokinetic (PK) study with limited toxicology endpoints in Sprague-Dawley rats, 2 repeat-dose CCI toxicology studies in Sprague-Dawley rats and cynomolgus monkeys, an in vitro cytokine release study using human PBMCs, and an in vitro off-target binding study using human HEK293 cells. The in vivo toxicology studies of CHS-388 were conducted in rats and cynomolgus monkeys, which were the only species identified as pharmacologically relevant based on CHS-388 avidity for IL-27. All in vivo toxicology studies were conducted by the CCI route of administration, which is the proposed

clinical route of administration. The pivotal toxicology studies were conducted in accordance with Good Laboratory Practice (GLP) regulations.

The weight of evidence from all the pharmacology and toxicology studies conducted with CHS-388 in vitro and in vivo supports its safety in the treatment of patients with advanced cancer. All of the in vivo safety studies conducted with CHS-388 resulted in no significant findings up to CCl mg/kg in both species, corresponding to an average serum maximum concentration (C_{max}) of CCl $\mu\text{g/mL}$ and area under the concentration versus time curve (AUC) from the start of dose administration to 168 hours postdose ($\text{AUC}_{[0-168]}$) of CCl h* $\mu\text{g/mL}$ in rats and C_{max} of CCl $\mu\text{g/mL}$ and $\text{AUC}_{(0-168)}$ of CCl h* $\mu\text{g/mL}$ in monkeys after repeat dosing.

CHS-388 is not a direct immune system agonist but instead antagonizes the cytokine IL-27 pathway by decreasing the amount of biologically active IL-27. No CCl changes were attributed to CHS-388 in vivo in the 4-week GLP toxicology study in cynomolgus monkeys. In an in vitro CCl assay using PBMCs isolated from healthy human donors, CHS-388 induced dose-dependent increases in interleukin-1 beta CCl at concentrations ranging from CCl $\mu\text{g/mL}$, while there were no noteworthy CCl changes between CCl and CCl $\mu\text{g/mL}$. The CHS-388 concentrations of CCl and CCl $\mu\text{g/mL}$ were approximately CCl and CCl , respectively, over the projected C_{max} at a human starting dose of CCl mg/kg.

In the 4-week GLP toxicology study in cynomolgus monkeys, CHS-388 caused decreases in the thyroid follicular size at $\geq \text{CCl}$ mg/kg that were considered not adverse. There were no corresponding changes in thyroid hormones (thyroid stimulating hormone [TSH], triiodothyronine 3 [T3], and thyroxine 4 [T4]) at any dose. The significance of these changes is unclear, and thyroid hormones in patients will be monitored in the clinic.

Further details on the nonclinical development of CHS-388 are available in the current version of the CHS-388 Investigator's Brochure.

1.3.2. Summary of Clinical Studies of CHS-388

Currently, there is one other ongoing CHS-388 clinical trial (SRF388-101, NCT04374877), a Phase 1, open-label, first-in-human, trial of CHS-388 monotherapy in patients with advanced solid tumors. The study consists of an initial monotherapy dose-escalation component followed by monotherapy expansions in specific tumors (eg, HCC, RCC) and a combination component (CHS-388 + pembrolizumab).

As of April 2021, 21 patients have been treated with CHS-388 at doses ranging from CCl to CCl mg/kg in Part A (dose-escalation component).²² Most patients were female (67%) with an Eastern Cooperative Oncology (ECOG) performance status of 1 (71%). The dose-escalation cohort was a heavily pretreated population, with > 50% having received ≥ 4 prior lines of therapy and 81% having had prior PD-1 pathway blockade. The Safety Analysis Set included all patients who received any amount of study medication. No dose-limiting toxicities have been observed to date. While 71% of patients experienced ≥ 1 treatment-emergent adverse events (TEAEs), only 19% experienced TEAEs that were assessed as related by Investigators. Low-grade fatigue was the most common treatment-related adverse event (AE), occurring in 2 patients, while the following treatment-related AEs were reported in 1 patient each: nausea, excess salivation, cough, and hyperthyroidism. There were no Grade ≥ 3 treatment-related AEs

or treatment discontinuations attributed to CHS-388. There was no related liver toxicity reported. There has been a confirmed partial response in a patient with advanced squamous cell non-small cell lung cancer whose disease had not responded to 3 prior standard therapies including platinum and taxane chemotherapy or PD-1 blockade, as well as evidence of disease stabilization in multiple patients. One patient with RCC who received prior anti-PD-1 treatment has had prolonged stable disease (SD) for > 9 months.

Safety Data Per Dose Level

As of April 2021, of the 6 patients who received the CC1 mg/kg once every 4 weeks (q4 weeks) dose selected as the recommended Phase 2 dose, 4 patients experienced at least one TEAE and 2 patients experienced Grade 3 or higher TEAEs. There were no TEAEs leading to treatment discontinuation. One patient at the CC1 mg/kg dose level died due to progressive disease (PD), which was considered a manifestation of underlying disease and not related to study drug.

An overview of TEAEs per dose level from the monotherapy dose escalation portion of the study is presented in [Table 4](#), with the CC1 mg/kg q4 weeks dose level column outlined. A summary of Grade 3 or higher TEAEs per dose level is presented in [Table 5](#).

Table 4: Overview of TEAEs Per Dose Level

TEAEs ^a per dose level, n (%)	CHS-388 CCI	CHS-388	CHS-388	CHS-388	CHS-388	CHS-388	CHS-388	Overall N = 21
	N = 1	N = 1	N = 1	N = 3	N = 3	N = 6	N = 6	
At least one TEAE	1 (100)	1 (100)	1 (100)	2 (66.7)	2 (66.7)	4 (66.7)	4 (66.7)	15 (71.4)
Serious TEAEs	0	0	0	1 (33.3)	0	1 (16.7)	2 (33.3)	4 (19.0)
TEAEs related to study drug ^b	0	0	1 (100)	1 (33.3)	0	1 (16.7)	1 (16.7)	4 (19.0)
Serious TEAEs related to study drug	0	0	0	0	0	0	0	0
AEs of special interest	0	0	0	0	0	0	0	0
TEAEs leading to DLTs	0	0	0	0	0	0	0	0
TEAEs leading to treatment discontinuation	0	0	0	0	0	0	0	0
Related TEAEs leading to treatment discontinuation	0	0	0	0	0	0	0	0
Treatment emergent lab abnormalities related to study drug	0	0	0	0	0	0	1 (16.7)	1 (4.8)
≥ Grade 3 TEAEs	0	0	0	1 (33.3)	1 (33.3)	2 (33.3)	2 (33.3)	6 (28.6)
TEAEs leading to Deaths	0	0	0	0	0	0	1 (16.7)	1 (4.8)

Abbreviations: AE = adverse event; DLT = dose limiting toxicity; TEAE = treatment-emergent adverse event.

^a TEAE is defined as an adverse event that emerges or worsens in the period from the first dose of CHS-388 to 30 days after the last dose.

^b TEAEs related to study drug is defined as a TEAE considered by the Investigator as possibly, probably, or definitely related to study drug.

Table 5: Summary of Grade 3 or Higher Treatment Emergent Adverse Events Regardless of Causality

Grade 3 or higher TEAEs ^a per dose level by Preferred Term, n (%)	CHS-388	CHS-388	CHS-388	CHS-388	CHS-388	CHS-388	CHS-388	Overall N = 21
	CCI N = 1	N = 1	N = 1	N = 3	N = 3	N = 6	N = 6	
At least one Grade 3 or higher TEAE	0	0	0	1 (33.3)	1 (33.3)	2 (33.3)	2 (33.3)	6 (28.6)
Ascites	0	0	0	0	0	0	2 (33.3)	2 (9.5)
Small intestinal obstruction	0	0	0	1 (33.3)	0	0	0	1 (4.8)
Fatigue	0	0	0	0	0	1 (16.7)	1 (16.7)	2 (9.5)
Disease progression	0	0	0	0	0	0	1 (16.7)	1 (4.8)
Urinary tract infection	0	0	0	0	0	0	1 (16.7)	1 (4.8)
Lymphocyte count decreased	0	0	0	0	0	1 (16.7)	0	1 (4.8)
Dyspnoea	0	0	0	0	1 (33.3)	0	0	1 (4.8)
Pleural effusion	0	0	0	0	0	0	1 (16.7)	1 (4.8)

Abbreviation: TEAE = treatment-emergent adverse event.

^a TEAE is defined as an adverse event that emerges or worsens in the period from the first dose of CHS-388 to 30 days after the last dose.

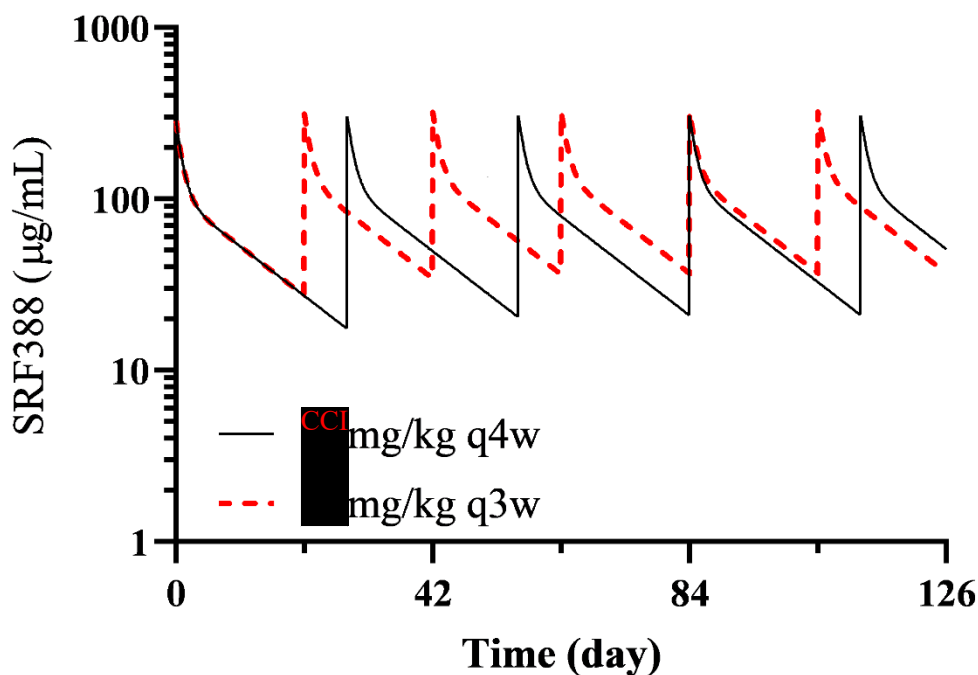
CHS-388 PK were linear and dose proportional, with an estimated half-life of approximately 12 days, ranging from 6 to 19 days. There is evidence of accumulation, with steady state reached by Cycle 3 and no anti-drug antibody (ADA) development to date. Maximum inhibition of the IL-27 signaling pathway as measured by > 90% pSTAT inhibition in whole blood was achieved starting at **CC1** mg/kg.

1.3.3. Pharmacokinetic Modeling for Dosing Once Every 3 Weeks

The planned dosing schedule for CHS-388 in Trial SRF388-201 is once every 3 weeks (q3 weeks). Prior to this study, CHS-388 has been investigated in Trial SRF388-101 Part A, with a dosing schedule of q4 weeks. To evaluate the potential PK difference between q3 and q4 week schedules, a PK model was established, simulations were performed, and PK parameters were compared. The PK model was established based on the observed PK data from patients in the **CC1** mg/kg dose level. The simulations were performed to evaluate the PK exposure, including C_{max} , trough concentration (C_{trough}), and AUC, after a single dose and at steady state. The model-simulated PK profiles are shown in [Figure 6](#) and the derived PK parameters are shown in [Table 6](#).

The model-simulated CHS-388 PK profiles were found to be similar between q3 week and q4 week dose schedules. The model-derived PK parameters were compared, and the minimum difference was anticipated between 2 dose schedules after a single dose. The PK parameters of CHS-388 at steady state were also evaluated, and the model predicted incremental differences between the 2 dose schedules (the q3 week schedule shows approximately 5% higher C_{max} and 15% higher AUC compared with the q4 week dose schedule). The predicted PK parameter difference was within typical interpatient variability and was considered comparable. Although the predicted C_{trough} was greater in the q3 week dose schedule (37 $\mu\text{g/mL}$) when compared to that in the q4 week schedule (21 $\mu\text{g/mL}$), it should be noted that one patient in Trial SRF388-101 who received **CC1** mg/kg q4 weeks had a measured CHS-388 level up to 80.8 $\mu\text{g/mL}$, and CHS-388 at this dose schedule was deemed safe and tolerable. Overall, the PK modeling suggests a minimum difference in PK parameters between the q3 week and q4 week dose schedules.

Figure 6: Model simulated PK profiles of CHS-388 with q3 week and q4 week dose schedules



Abbreviations: q3w = once every 3 weeks; q4w = once every 4 weeks.

Table 6: Model Predicted PK Parameters of CHS-388 With q4 Week and q3 Week Dose Schedules

Model Predicted PK Parameters	100 mg/kg q4 week	100 mg/kg q3 week
Single Dose		
$C_{\max}$ (µg/mL)	285	285
$AUC_{21 \text{ day}}$ (day·µg/mL)	2871	2871
C_{trough} (µg/mL)	18	18
Steady State		
$C_{\max}$ (µg/mL)	306	322
$AUC_{21 \text{ day}}$ (day·µg/mL)	3178	3651
C_{trough} (µg/mL)	21	37

Abbreviations: $AUC_{21 \text{ day}}$ = area under the concentration versus time curve from 0 to 21 days; $C_{\max}$ = maximum concentration; C_{trough} = minimum concentration; PK = pharmacokinetic(s); q3 week = once every 3 week(s); q4 week = once every 4 week(s).

1.4. Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody that is produced in Chinese hamster ovary cells. Atezolizumab targets PD-L1 on tumor-infiltrating immune cells or tumor cells and prevents interaction with the PD-1 receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a nonglycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc effector function. By eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity, antibody-mediated clearance of activated effector T cells is also eliminated.

Expression of PD-L1 is prevalent among many human tumors,²³ and its overexpression is associated with poor prognosis for patients with certain cancers.²⁴⁻²⁷ Therefore, interruption of the PD-L1/PD-1 pathway represented an attractive strategy to reinvigorate tumor-specific T cell immunity and is now proven to improve clinical outcomes across multiple solid tumors including regulatory approval in HCC, urothelial carcinoma, non-small cell lung cancer, small cell lung cancer, triple-negative breast cancer, and melanoma (Tecentriq[®] Prescribing Information, 2021).⁴²

1.5. Bevacizumab

Bevacizumab is a recombinant humanized IgG1 monoclonal antibody that binds VEGF, a secreted factor that stimulates angiogenesis. Increased levels of VEGF expression have been found in most human malignancies examined to date,²⁸⁻³⁰ and increased VEGF serum levels have been correlated with poor survival.

Bevacizumab prevents the interaction of VEGF with its receptors and neutralizes the biological activity of VEGF. Bevacizumab was generated by humanization of the murine parent antibody A4.6.1.³¹ Primary pharmacology studies demonstrated that administration of A4.6.1 to tumor-bearing animals resulted in increased host survival secondary to tumor growth inhibition.³²⁻³⁵ This therapeutic strategy of neutralizing a growth factor was the first direct experimental evidence that solid tumor growth was dependent on the formation of new blood vessels.³⁴ Furthermore, this strategy demonstrated that VEGF is a key regulator of tumor-associated blood vessel formation and that inhibition of VEGF results in reduced tumor growth.

1.6. Atezolizumab + Bevacizumab in HCC

Combined inhibition of PD-L1 and VEGF has demonstrated antitumor activity in HCC.⁵ VEGF has been implicated as a causative factor in patients with HCC who develop PD.³⁶⁻³⁸ The efficacy of anti-PD-1 and anti-PD-L1 may be enhanced by the reversal of VEGF-mediated immunosuppression and promotion of T-cell infiltration within the tumor microenvironment by anti-VEGF therapies.^{39, 40} The combination of atezolizumab and bevacizumab has demonstrated durable antitumor responses and improved PFS in patients with advanced, unresectable HCC.^{5, 41}

Initially, a Phase 1b open-label trial investigated the safety and efficacy of atezolizumab in combination with bevacizumab and/or other treatments in patients with solid tumors.⁴¹ Cohort F of this trial randomized patients with advanced or metastatic and/or unresectable HCC who had received no prior systemic treatment in a 1:1 ratio to receive atezolizumab plus bevacizumab or atezolizumab alone q3 weeks. Median PFS was significantly improved at 5.6 months (95% CI, 3.6-7.4 months) in the atezolizumab plus bevacizumab group versus 3.4 months with atezolizumab monotherapy (95% CI, 1.9-5.2 months; HR 0.55, 80% CI 0.40-0.74, $p = 0.011$). Confirmed ORRs were 20% (95% CI, 11% to 32%) and 17% (95% CI, 8% to 29%), respectively. Median OS was not reached in either treatment group; 27% of patients in the combination therapy group and 31% of patients in the monotherapy group had died at the time of the data cutoff. There were no deaths related to study treatment. However, 12% of the patients experienced serious adverse events (SAEs) that were considered related to study treatment. The most common treatment-related Grade 3 AEs (occurring in > 15% of patients) in the atezolizumab plus bevacizumab group were hypertension and proteinuria at 5%, whereas the most common treatment-related Grade 3 AE (occurring in > 15% of patients) in the atezolizumab monotherapy group was increased aspartate aminotransferase at 3%.

A confirmatory Phase 3 trial showed significantly improved OS, PFS, and ORR with the combination of atezolizumab plus bevacizumab compared to standard of care sorafenib in patients with advanced unresectable HCC who had not received any prior systemic therapy.⁵ Patients were randomized in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. Atezolizumab plus bevacizumab significantly improved OS at 12 months compared to sorafenib: 67.2% (95% CI, 61.3%-73.1%) vs. 54.6% (95% CI, 45.2%-64.0%), respectively. Median PFS was 6.8 months (95% CI, 5.7-8.3 months) in the atezolizumab plus bevacizumab group and 4.3 months (95% CI, 4.0-5.6 months) in the sorafenib group. The confirmed ORRs were 27.3% (95% CI, 22.5%-32.5%) with atezolizumab plus bevacizumab and 11.9% (95% CI, 7.4%-18.0%) with sorafenib, per independent assessment with RECIST 1.1 ($p < 0.001$), and 33.2% (95% CI, 28.1%-38.6%) and 13.3% (95% CI, 8.4%-19.6%), respectively, according to HCC-specific modified RECIST (mRECIST) ($p < 0.001$). Of the responders, 18 patients (5.5%) in the atezolizumab plus bevacizumab group experienced a CR; no patient in the sorafenib group had a CR. The most common AEs (occurring in $\geq 20\%$ of patients) in the atezolizumab plus bevacizumab group were hypertension (29.8%), fatigue (20.4%), and proteinuria (20.1%); the most common AEs in the sorafenib group were diarrhea (49.4%), palmar-plantar erythrodysesthesia syndrome (48.1%), hypertension (24.4%), and decreased appetite (24.4%). The most common Grade 3 or Grade 4 event was hypertension (15.2% in the atezolizumab plus bevacizumab group). Patient-reported outcomes indicated a longer time to deterioration of quality of life among patients who received atezolizumab plus bevacizumab compared with patients who received sorafenib. The toxicity-related events were in keeping with the known safety profiles of these medications, as no unexpected safety signals were detected in this Phase 3 trial.

In an updated analysis of the Phase 3 trial, with a median follow-up of 15.6 months, median OS was 19.2 months (95% CI, 17.0-23.7 months) in the atezolizumab plus bevacizumab compared with 13.4 months (95% CI, 11.4-16.9 months) with sorafenib (HR 0.66, 95% CI 0.52-0.85; $p = 0.0009$).⁶ Median PFS was 6.9 months (95% CI, 5.7-8.6 months) in the atezolizumab plus bevacizumab group and 4.3 months (95% CI, 4.0-5.6 months) in the sorafenib group (HR 0.65, 95% CI 0.53-0.81; $p = 0.0001$). The confirmed ORRs were 30% (95% CI, 25%-35%) with atezolizumab plus bevacizumab and 11% (95% CI, 7%-17%) with sorafenib, per independent assessment with RECIST 1.1 and 35% (95% CI, 30%-41%) and 14% (95% CI, 9%-20%), respectively, according to mRECIST.

Additional details on atezolizumab, bevacizumab, and the combination are available in the current versions of the atezolizumab and bevacizumab Investigator's Brochures.

1.7. Study Rationale

Atezolizumab plus bevacizumab is a standard of care for patients with unresectable or metastatic HCC who have not received prior systemic therapy.^{5, 42}

IL-27 is an immunoregulatory cytokine that limits the intensity and duration of T-cell responses associated with chronic infection and cancer. When bound to its receptor, IL-27 mediates reductions in anticancer pro-inflammatory cytokine secretion and increased expression of inhibitory checkpoint receptors such as PD-L1, TIM-3, LAG3, and TIGIT through the JAK-STAT pathway.¹³⁻¹⁷ CHS-388 blocks the cytokine from binding to its receptor, resulting in subsequent immune activation in the tumor microenvironment and tumor growth inhibition in multiple preclinical models.^{13, 43}

In vitro, CHS-388 inhibits IL-27-induced expression of T cell exhaustion markers such as PD-L1 and TIM-3 on human primary immune cells. Both as a single agent and in combination with anti-PD-1 treatment, CHS-388 reverses the anti-inflammatory actions of IL-27 and promotes immune cell activation by inducing antitumor cytokine production (eg, $\text{TNF}\alpha$ and $\text{IFN}\gamma$) in PBMC cultures from healthy donors and patients with cancer.⁴³ In a model of established HCC, CHS-388 substantially inhibited tumor growth in a dose-dependent manner, led to a reduction in the expression of genes associated with tumor burden (eg, alpha-fetoprotein [AFP]) and immune inhibitory receptors (eg, PD-L1, TIGIT), repressed transcripts associated with transforming growth factor beta signaling, and altered myeloid and NK cell transcripts.²⁰ Mechanistically, inhibition of IL-27 signaling can promote increased antigen-specific CD4+ and CD8+ T-cell responses,¹² and IL-27 can also serve as a checkpoint for NK cells and impact their ability to control HCC development in mouse models.⁴⁴ Genetic loss of the IL-27 receptor suppresses HCC development in both toxin/carcinogen-induced diethylnitrosamine and NASH-driven models.⁴⁴ Mechanistic studies show that loss of IL-27 signaling results in NK cell accumulation and activation within the HCC tumors that prohibit tumor growth.

CCI we hypothesize that the addition of CHS-388 to atezolizumab plus bevacizumab will enhance response to PD-1 pathway blockade by counteracting IL-27 immunosuppression in the tumor microenvironment of HCC, a tumor for which IL-27 may play a role in pathogenesis and/or resistance.^{20, 43} This multicenter Phase 2 trial will evaluate the clinical benefit of adding CHS-388 to atezolizumab plus bevacizumab in first-line HCC.

1.8. Selection of Patient Population

The population to be studied in this Phase 2 trial includes patients with first-line advanced or metastatic HCC who are eligible for standard-of-care atezolizumab plus bevacizumab.

1.9. Determination of Dose and Schedule

Atezolizumab and bevacizumab will be administered on a q3 week schedule and at the standard doses of **CC1** mg **CC1** q3 weeks and **CC1** mg/kg **CC1** q3 weeks, respectively. CHS-388 will be given at **CC1** mg/kg q3 weeks. The dose of **CC1** mg/kg was selected based on safety, PK, pharmacodynamics, and early efficacy signal of CHS-388 observed in the dose-escalation component (Part A) of the SRF388-101 trial. CHS-388 PK are linear and dose-proportional across all dose levels tested, with safe levels of accumulation and no ADA formation to date. Pharmacodynamic data show evidence of peripheral target inhibition with maximal target inhibition of IL-27 mediated pSTAT1 throughout the dosing interval.

To align with the atezolizumab and bevacizumab dose schedule, the CHS-388 dose schedule has been modified to q3 weeks from q4 weeks in Part A of Trial SRF388-101. The **CC1** mg/kg dose with a q4 week schedule has been cleared in the SRF388-101 clinical trial, with dose escalation ongoing. PK modeling was performed to evaluate the impact of different dose schedules on CHS-388 exposure. The results showed only incremental PK differences between q3 week and q4 week schedules. The current safety data and PK modeling support that **CC1** mg/kg may be safely given on a q3 week schedule. CHS-388 will be administered prior to atezolizumab and bevacizumab.

The Safety Lead-In will confirm the preliminary safety and tolerability of the triplet combination. All 6 patients treated at the specified dose level will receive 1 cycle of the triplet combination and safety stopping rules will be applied for safety evaluation (see Section 4.1.1 for details). Once the Safety Lead-In of the triplet therapy has met criteria to move forward, approximately 24 additional patients will be treated in the Lead-In Expansion, which will continue to evaluate safety as well as preliminary efficacy. A Safety Review Committee (SRC) will be utilized to regularly review all accumulated safety, PK, pharmacodynamics when appropriate, and preliminary efficacy during the Lead-In.

2. OBJECTIVES

All objectives are for both the Lead-In and Randomized Phase unless otherwise specified.

2.1. Primary Objectives

Lead-In:

- To evaluate the safety and tolerability of CHS-388 in combination with atezolizumab + bevacizumab

Randomized Phase:

- To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab as measured by PFS

2.2. Secondary Objectives

2.2.1. Efficacy Objectives

- To evaluate preliminary measures of efficacy of CHS-388 in combination with atezolizumab + bevacizumab in the Lead-In
- To evaluate additional measures of efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab in the Randomized Phase
- To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab according to serum EBI3 levels in the Lead-In
- To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab according to serum EBI3 levels in the Randomized Phase

2.2.2. Safety Objective

- To evaluate the safety and tolerability of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab in the Randomized Phase

2.2.3. Immunogenicity Objectives

- To characterize the immunogenicity of CHS-388 and atezolizumab
- To explore potential correlations between immunogenicity and efficacy, safety, and PK outcomes

2.2.4. Pharmacokinetic Objectives

- To characterize the PK profile of CHS-388 when given in combination with atezolizumab + bevacizumab
- To explore the potential PK impact from drug interaction

2.3. Exploratory Biomarker Objectives

- To identify and evaluate potential blood or tissue biomarkers of response, resistance, and/or safety
- To evaluate the effects of CHS-388 in combination with atezolizumab + bevacizumab on peripheral blood immune cell subsets and circulating cytokines and chemokines

3. ENDPOINTS

All endpoints are for both the Lead-In and Randomized Phase unless otherwise specified.

3.1. Primary Endpoints

Lead-In:

- Nature, frequency, and severity of AEs per National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher
- Timing of AEs

Randomized Phase:

- PFS, defined as time from randomization to occurrence of PD or death from any cause (whichever occurs first), as determined by Investigator review according to RECIST v1.1

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

- PFS, defined as time from study drug initiation to occurrence of PD or death from any cause (whichever occurs first), as determined by Investigator review according to RECIST v1.1 (Lead-In only)
- PFS, defined as time from study drug initiation (Lead-In) or randomization to occurrence of PD or death from any cause (whichever occurs first), as determined by Investigator review according to HCC mRECIST
- ORR as determined by Investigator review according to:
 - RECIST v1.1
 - HCC mRECIST
- Duration of response (DoR), defined as time from initial documented objective response to PD or death from any cause (whichever occurs first), as determined by Investigator review according to:
 - RECIST v1.1
 - HCC mRECIST
- Disease control rate (DCR), defined as the proportion of patients who experience best overall response of complete response (CR), partial response (PR), or SD
- Time to progression (TTP), defined as time from study drug initiation (Lead-In) or randomization to occurrence of disease progression, as determined by Investigator review according to:
 - RECIST v1.1
 - HCC mRECIST

- OS, defined as time from study drug initiation (Lead-In) or randomization to death from any cause
- Time to response, defined as time from study drug initiation (Lead-In) or randomization to initial documented objective response, as determined by Investigator review according to:
 - RECIST v1.1
 - HCC mRECIST
- Time on therapy, defined as time from study drug initiation (Lead-In) or randomization to last treatment
- PFS, ORR, TTP, and OS by serum EBI3 concentrations

3.2.2. Safety Endpoints

Randomized Phase:

- Nature, frequency, and severity of AEs per National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher
- Timing of AEs

3.2.3. Immunogenicity Endpoints

- Incidence of CHS-388 ADAs
- Incidence of atezolizumab ADAs
- Efficacy, safety, and PK endpoints by ADA status

3.2.4. Pharmacokinetic Endpoints

- Serum concentrations of CHS-388
- Serum concentrations of atezolizumab

3.3. Exploratory Biomarker Endpoints

- Assessment of selected blood-based and tumor tissue biomarkers, which may include cytokines, immune cell population subset enumeration and evaluation, PD-L1 expression, gene and protein expression levels, DNA mutation and copy number variations, and correlation of Baseline levels and changes in these markers with clinical outcomes (eg, PFS, ORR)
- Changes in peripheral blood immune cell populations by flow cytometry and gene expression

4. TRIAL DESIGN

SRF388-201 is a Phase 2 trial composed of a Lead-In followed by a Randomized Phase designed to evaluate the efficacy and safety of CHS-388 in combination with atezolizumab plus bevacizumab (Arm A) compared to placebo in combination with atezolizumab plus bevacizumab (Arm B) in patients with first-line advanced or metastatic HCC.

After a Safety Lead-In of 6 patients who will receive open-label CHS-388 + atezolizumab + bevacizumab, approximately 24 additional patients will be enrolled in the Lead-In Expansion. The Randomized Phase follows the Lead-In Expansion and will randomize approximately 104 patients with a 1:1 allocation to Arm A or Arm B and stratified by geographic region (Asia excluding Japan vs. rest of world) and Barcelona Clinic Liver Cancer (BCLC) stage (B or C).

4.1. Lead-In

4.1.1. Safety Lead-In

Six patients will be enrolled in a Safety Lead-In to assess the preliminary safety and tolerability of the triplet combination. Patient dosing will be staggered by 48 hours during the Safety Lead-In and all patients will receive CHS-388 + atezolizumab + bevacizumab **CCI** q3 weeks on Day 1 of a 21-day cycle. During the Safety Lead-In, all 6 patients will receive 1 cycle of the triplet combination, during which safety stopping rules will be applied for safety evaluation. If 2 or more of these 6 patients experience a Grade ≥ 3 related AE (with the exception of toxicities listed in [Table 7](#)), any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1, or prolonged delay (defined as > 14-day delay in initiating Cycle 2 due to toxicity), the trial will be halted for safety review with consideration given for evaluating an additional 6 patients at a reduced dose of CHS-388 in conjunction with atezolizumab + bevacizumab. If < 2 patients experience a Grade ≥ 3 related AE as defined by the safety stopping rules, any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1, or prolonged delay (defined as > 14-day delay in initiating Cycle 2 due to toxicity), then approximately 24 additional patients will be enrolled in the Lead-In Expansion before the study will move forward into the Randomized Phase. The goal of the safety evaluation for the triplet is to evaluate for any signal of unexpected or increased toxicities when given together that would not be observed with any agent alone. As such, a Grade ≥ 3 toxicity known to be associated with any of the 3 study drugs' established safety profiles would not be considered concerning.

Table 7: Stopping Rule Exceptions for the Safety Lead-In

The following Grade ≥ 3 toxicities considered at least possibly related to study treatment would not be considered to meet criteria for a safety stopping rule:	
Nausea	Any Grade ≥ 3 event responding to supportive treatment within 3 days
Vomiting	
Diarrhea	
Fatigue	Grade ≥ 3 lasting < 7 days
Hypertension	Grade ≥ 3 lasting any duration if can be controlled with treatment
Proteinuria	Grade ≥ 3 lasting < 14 days
Asymptomatic amylase/lipase elevations	Grade ≥ 3 lasting any duration if asymptomatic/ no clinical signs of pancreatitis
Thyroid function abnormalities (eg, hypo- or hyperthyroidism)	Grade ≥ 3 lasting any duration if can be controlled with treatment such as thyroid supplementation or beta blockade
Rash	Grade ≥ 3 recovering to Grade 1 with treatment (ie, steroids) within 7 days
Alopecia	Grade ≤ 2 lasting any duration
Non-hematologic laboratory abnormalities	Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, electrolytes, uric acid, etc.

To be considered evaluable for the Safety Lead-In, patients must have completed at least 50% of the prescribed doses of all 3 drugs during the review period (Day 1-21 = Cycle 1) and must not have discontinued treatment during Cycle 1 for reasons other than drug-related AEs. For example, patients who discontinued study treatment during Cycle 1 for PD or for patient or physician preference but without experiencing a Grade ≥ 3 related toxicity would not be considered fully evaluable for the Safety Lead-In and would be replaced. A ‘related’ toxicity is defined as those toxicities assessed by the Investigator to be possibly, probably, or definitely related to any study drug.

This analysis set will be used to assess the preliminary safety of the triplet therapy.

4.1.2. Lead-In Expansion

Once the Safety Lead-In of the triplet therapy has met criteria to move forward, the Lead-In will be expanded to enroll approximately 24 additional patients. All patients will receive CHS-388 + atezolizumab + bevacizumab CC1 q3 weeks on Day 1 of a 21-day cycle.

The full Lead-In Analysis Set (Safety Lead-In plus Lead-In Expansion) will be used to further assess the safety of the triplet as well as to evaluate the preliminary efficacy.

4.1.3. Safety Review Committee

The Lead-In (Safety Lead-In and Lead-In Expansion) portion of the study will utilize an SRC, which will meet regularly to review all accumulated data, including safety, PK, pharmacodynamics when appropriate, and preliminary efficacy. The SRC will be composed of a medical representative from the Sponsor, a Medical/Safety Monitor from the Contract Research Organization supporting the trial (if applicable), and all Principal Investigators (or their specified delegates) at each of the enrolling sites. Furthermore, the SRC will be responsible for periodic safety review throughout the treatment period for the Lead-In (Safety Lead-In and Lead-In

Expansion), including an assessment of toxicities once all enrolled patients in the Safety Lead-In have completed 1 cycle of treatment. The SRC may recommend pausing enrollment, discontinuing, or expanding any portion of the Lead-In at any time based on a comprehensive review of all clinical data.

4.2. Randomized Phase

During the Randomized Phase, central treatment allocation/randomization will occur using Interactive Response Technology (IRT). There are 2 treatment arms and patients will be assigned randomly in a 1:1 fashion to Arm A (CHS-388 + bevacizumab + atezolizumab) or Arm B (placebo + bevacizumab + atezolizumab). Dosing should occur within 1 week of randomization. If a patient discontinues from the trial, the patient identifier will not be reused and the patient will not be allowed to re-enter the trial.

4.2.1. Independent Data Monitoring Committee

An IDMC will be assembled to periodically review all available safety information. Once the first patients enrolled in the Randomized Phase (~10 patients per arm) have completed 1 cycle of treatment, the IDMC will review the safety data. Trial enrollment will continue without pause during IDMC data review of these first 20 patients as well as during subsequent periodic IDMC safety reviews. The IDMC will also review efficacy data at the planned interim analysis. Based on the review of all available data, the IDMC will recommend one of the following actions for the trial: continue as planned, continue with modifications, or stop early.

The IDMC will also review the interim analysis for futility once approximately 50% of the expected PFS events occur. Periodic IDMC data reviews will continue approximately every 4 to 6 months during study conduct.

The Sponsor will make all final decisions regarding any changes in study conduct, taking into account the IDMC recommendations. Membership and responsibilities of the IDMC will be described in a separate IDMC Charter.

4.3. Dosing Frequency

CHS-388/placebo will be administered in combination with atezolizumab and bevacizumab in 21-day cycles according to the following dosing schedule:

In Lead-In and in Randomized Phase Arm A (CHS-388 + atezolizumab + bevacizumab), CHS-388 ^{CC1} mg/kg ^{CC1} will be administered first. After an observation period of 30 minutes, the other study drugs may be administered. Atezolizumab ^{CC1} mg ^{CC1} should be administered prior to bevacizumab ^{CC1} mg/kg ^{CC1}

In Randomized Phase Arm B (placebo + atezolizumab + bevacizumab), placebo ^{CC1} will be administered first. After an observation period of 30 minutes, the other study drugs may be administered. Atezolizumab ^{CC1} mg ^{CC1} should be administered prior to bevacizumab ^{CC1} mg/kg ^{CC1}

See Section 7 for additional details regarding the order and timing of study drug administration.

4.4. Monitoring of Adverse Events

Patients will be monitored continuously for toxicity while on study treatment. The severity of AEs will be assessed using the NCI-CTCAE version 5.0 or higher by the site Investigators. If a patient has an AE of particular severity or an AE that is considered at least possibly related to study drug (CHS-388/placebo, atezolizumab, and/or bevacizumab), then dose modifications will be made according to the guidelines set forth in the trial protocol (see Section 7.2 and Section 7.5).

4.5. Blinding and Unblinding

4.5.1. Blinding

This trial will be blinded with respect to treatment assignment. Patients, Sponsor study team members, vendor personnel, Investigators, and investigative site personnel other than an unblinded pharmacist will be blinded to the treatment assigned to each patient during the trial. See Section 7.1.3 for details on CHS-388/placebo blinding.

Sponsor and employees acting on behalf of the Sponsor may have access to unblinded safety reports due to regulatory safety reporting requirements. Every effort will be made to minimize the number of Sponsor staff unblinded to treatment assignments for this purpose.

4.5.2. Unblinding

A patient's treatment assignment may need to be unblinded in certain circumstances, such as a medical emergency, when the unblinding of the study drug is essential for the clinical management or safety of the patient. Unblinding may also be necessary if a female patient (or a male patient's partner) becomes pregnant during the trial or within 6 months of the last dose of blinded study drug.

The Investigator must contact the Medical Monitor for discussion and approval prior to unblinding the patient's treatment assignment. If the Investigator determines that the patient is in imminent danger and treatment assignment must be known immediately, and an attempt to reach the Medical Monitor has been unsuccessful, the Investigator may unblind the patient prior to informing the Medical Monitor.

Unblinding requests should be made by the site Investigator through the IRT system; please see the SRF388-201 IRT User Manual for details. The Sponsor will not provide randomization codes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary, for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary.

In the event that unblinding occurs, the circumstances around the unblinding (eg, date and reason) must be documented promptly. Only the Principal Investigator or delegate and the respective patient's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

Where required by local regulation, expedited reporting of SAEs to specific regulatory authorities and/or ethics committees will include information regarding the study drug treatment assignment. Only the Sponsor staff and employees acting on behalf of the Sponsor responsible for expedited safety reporting will be unblinded to treatment assignments for this purpose.

4.6. Treatment Beyond Progression

Patients may continue on treatment past radiologic progression if deemed clinically appropriate and safe by the Investigator. To continue study therapy past progression of disease, the following criteria indicating evidence of clinical benefit must be met:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status from study entry
- Absence of symptomatic or rapid disease progression requiring urgent medical intervention

Prior to continuing study therapy past radiologic progression, patients will be re-consented and adequately informed of alternative available Food and Drug Administration-approved therapies, the potential clinical risks and benefit, and that the patient may be foregoing these options in order to continue receiving the investigational products which may not provide additional clinical benefit.

Patients who remain on study past progression should have a confirmatory scan after at least 4 weeks but not more than 9 weeks later.

4.7. Treatment Discontinuation

Treatment discontinuation is defined as any patient who stops receiving study drug (CHS-388/placebo, atezolizumab, and/or bevacizumab) and does not restart CHS-388/placebo or bevacizumab within 42 days or atezolizumab within 12 weeks. A patient should be discontinued from the study drug if, in the opinion of the Investigator or Sponsor, it is medically necessary or if it is the wish of the patient. Discontinuation of study treatment does not represent withdrawal from the trial.

All patients should undergo the Safety Follow-up Visit when they discontinue the last study drug (Section 6.4).

Patients will be discontinued from all study drugs for any of the following reasons:

- AE(s) that requires permanent discontinuation of all study drugs
- Disease progression
- Noncompliance with protocol
- Investigator decision (specific justification to be documented)
- Patient becomes pregnant
- Patient lost to follow-up

- Termination of the study by the Sponsor
- Voluntary withdrawal by patient

The AEs leading to the discontinuation of study drug will be followed until resolution to Baseline or until the event is considered stable or chronic. Patients who discontinue treatment with any study drug for any reason, but who are deriving clinical benefit (objective response or stable disease) from 1 or both of the remaining drugs, may continue to receive those study drugs at the discretion of the Investigator and Sponsor.

The End of Treatment (EoT) Visit should occur within 7 days after a patient discontinues the last study drug. Disease response assessments conducted within the previous 30 days need not be repeated at EoT. Other assessments previously performed within the previous 2 weeks need not be repeated at EoT.

All patients will have a Safety Follow-up Visit at 30 (+ 5) days as well as a Long-term Follow-up Visit at 90 (+ 5) days after the last dose of study drug (CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later). If possible, this visit should occur before the initiation of any subsequent anticancer therapy. At a minimum, this visit should include collection of AEs/SAEs and concomitant medications/procedures. This can be performed by telephone call, if the patient does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case a clinic visit will be required.

For patients who discontinue study drug due to a treatment interruption of CHS-388/placebo and bevacizumab lasting > 42 days and atezolizumab lasting > 12 weeks, the EoT Visit should be completed as soon as possible. The Safety Follow-up Visit is not required for these patients; however, these patients must complete the Long-term Follow-up Visit and will be followed for survival.

Response assessments will be conducted per [Table 2](#) until the patient experiences PD or discontinues from the study (see [Section 6.3](#)).

4.8. Trial Withdrawal

Patients may voluntarily withdraw from the study at any time for any reason without prejudice.

Patients will be withdrawn from the study in case of any of the following reasons:

- Patient death
- Patient lost to follow-up
- Termination of the study by Sponsor
- Voluntary withdrawal of consent by patient

If the patient withdraws consent from the overall study participation (and not just study drug), no further evaluations should be performed, and no attempts should be made to collect additional data.

5. TRIAL POPULATION

5.1. Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. Patient is ≥ 18 years of age on day of signing informed consent.
2. Patient has unresectable locally advanced or metastatic HCC with diagnosis confirmed by histology/cytology or clinically by American Association for the Study of Liver Diseases (AASLD) criteria (see [Appendix 1](#)) in cirrhotic patients. Patients without cirrhosis require histological confirmation of diagnosis.
3. Patient has had no prior systemic treatment for unresectable locally advanced or metastatic HCC.
4. Patient has BCLC Stage B (not eligible for transcatheter arterial chemoembolization) or Stage C disease.
5. Patient has Child-Pugh Class A disease.
6. Patient has ≥ 1 measurable lesion per RECIST v1.1. Lesion(s) should be suitable for repeat measurement.

Note: Lesions previously treated with radiation or other forms of locoregional therapy must show radiographic evidence of PD to be designated as a target lesion.

7. Patient has an ECOG performance status of 0 or 1.
8. Patient has laboratory values indicative of adequate organ function (see [Table 8](#)).

Table 8: Laboratory Values Indicative of Adequate Organ Function Required for Inclusion in Trial SRF388-201

System/Parameter	Laboratory Value
Hematological	
ANC	$\geq 1500/\mu\text{L}$ ($1.5 \times 10^9/\text{L}$)
ALC	$\geq 500/\mu\text{L}$ ($0.5 \times 10^9/\text{L}$)
Platelets	$\geq 75,000/\mu\text{L}$ ($\geq 75 \times 10^9/\text{L}$) without platelet transfusion
Hemoglobin	$\geq 9.0 \text{ g/dL}^a$
Renal	
Creatinine OR CrCl ^b (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times \text{ULN}$ OR $\geq 50 \text{ mL/min}$ for patients with creatinine levels $> 1.5 \times \text{institutional ULN}$
Urinalysis for proteinuria	Proteinuria $< 2+$ (within 7 days prior to initiation of study treatment). If $\geq 2+$ proteinuria at Baseline, patient should undergo a 24-hour urine collection and must demonstrate $< 1 \text{ g}$ of protein in 24 hours.

System/Parameter	Laboratory Value
Hepatic	
Total bilirubin	$\leq 3 \times \text{ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 5 \times \text{ULN}$
ALP	$\leq 5 \times \text{ULN}$
Serum albumin	$\geq 2.8 \text{ g/dL}$ ($\geq 28 \text{ g/L}$)
Coagulation	
INR or PT aPTT	$\leq 2 \times \text{ULN}$ unless patient is receiving anticoagulant therapy. For patients receiving anticoagulant therapy, PT, aPTT, or INR should be within the therapeutic range of anticoagulants.
Endocrine	
Calcium	Ionized calcium $\leq 1.5 \text{ mmol/L}$ or calcium $\leq 12 \text{ mg/dL}$, and corrected serum calcium $< \text{ULN}$

Abbreviations: ALC = absolute lymphocyte count; ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; HCC = hepatocellular carcinoma; INR = international normalized ratio; PT = prothrombin time; ULN = upper limit of normal.

^a Criteria must be met without packed red blood cell transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin ($\geq$ approximately 3 months).

^b CrCl should be calculated using the Cockcroft-Gault formula:

$$(140 - \text{age [years]}) \times \text{weight [kg]} / \text{serum creatinine (mg/dL)} \times 72$$

9. For women of childbearing potential (WCBP): negative serum β human chorionic gonadotropin (β hCG) pregnancy test within 1 week prior to first dose of study drug (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for ≥ 12 consecutive months without an alternative medical cause).
10. WCBP must be willing to refrain from heterosexual intercourse or use acceptable methods of birth control while they are receiving study drug and for 6 months after the last dose of any study drug. Acceptable methods of birth control are described in Section 6.7.5. WCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, female patients must still undergo pregnancy testing as described in the Schedule of Assessments (Table 1 and Table 2).
11. Male patients must be willing to refrain from heterosexual intercourse with a partner of childbearing potential or a pregnant partner or use acceptable methods of birth control while they are receiving study drug and for 6 months after the last dose of any study drug to avoid exposing the embryo. Acceptable methods of birth control are described in Section 6.7.5. Men must refrain from donating sperm during this same period. Azoospermic male patients are exempt from contraceptive requirements.
12. Patient has the ability to adhere to the trial visit schedule and all protocol requirements.

13. Patient has provided signed and dated institutional review board/independent ethics committee-approved informed consent form before any Screening procedures are performed.

5.2. Exclusion Criteria

Patients are to be excluded from the trial if they meet any of the following criteria:

1. Patient is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
2. Patient has previously received an anti-IL-27 antibody (Ab) or anti-IL-27-targeted therapy.
3. Patient has received prior systemic therapy for unresectable or metastatic disease.

Note: Prior systemic therapies administered for neoadjuvant, adjuvant, or curative intent (localized disease) are permitted if they were given > 1 year prior to the development of recurrent or metastatic disease.

4. Patient has received prior local, neoadjuvant, or adjuvant anticancer therapy > 1 year ago but has not had resolution of any non-immune-related AEs (irAEs) secondary to prior anticancer therapy to Grade ≤ 1 per NCI-CTCAE version 5.0 or higher and/or complete resolution of any irAEs secondary to prior immune checkpoint inhibitor therapy, with the following exceptions:
 - a. Patients with non-irAEs of alopecia, peripheral neuropathy, stable thyroid dysfunction, Grade ≤ 2 controlled rash, and Grade ≤ 2 electrolyte abnormalities on a stable dose of supplementation are eligible even if these AEs have not resolved to Grade ≤ 1 per NCI-CTCAE version 5.0 or higher.
 - b. Patients with the following clinically stable or clinically nonsignificant irAEs are eligible: controlled thyroid disorders, vitiligo, asymptomatic elevated amylase/lipase, type 1 diabetes on insulin, Grade ≤ 2 controlled rash, and Grade ≤ 2 electrolyte abnormalities on a stable dose of supplementation.
 - c. Patients with other clinically stable or nonsignificant AEs from past therapy may be eligible with permission from the Sponsor.
 - d. Patients who discontinued prior treatment due to a Grade ≥ 3 irAE are excluded even if the event has resolved.
5. Patient has known fibrolamellar HCC histology, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.
6. Patient has moderate or severe ascites.
7. Patient has uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).

Note: Patients with indwelling catheters (eg, PleurX™) are eligible.
8. Patient has a history of or current hepatic encephalopathy.

9. Patient is unable to undergo disease evaluation with a triphasic computed tomography (CT) or magnetic resonance imaging (MRI) because of contrast allergy or other contraindication.
10. Patient has imaging findings consistent with $\geq 50\%$ liver occupation by HCC tumors.
11. Patient has untreated or incompletely treated varices with bleeding or high risk for bleeding.

Note: Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone EGD within 6 months of study treatment initiation do not need to repeat the procedure.

12. Patient has a history of Grade 4 allergic or anaphylactic reaction to any monoclonal antibody therapy or any excipient in the study drugs.
13. Patient has undergone a major surgical procedure, other than for diagnosis, within 28 days prior to initiation of study treatment, or anticipates the need for a major surgical procedure during the trial.
14. Patient has not fully recovered from surgical resection or ablation within 4 weeks prior to randomization.
15. Patient has symptomatic or untreated brain metastases or leptomeningeal carcinomatosis.

Note: Patients previously treated for brain metastases must be ≥ 28 days from completion of radiation treatment, with follow-up imaging showing no progression, and have no ongoing steroid requirement.

16. Patient has received a prior allogeneic hematopoietic cell transplant or solid tumor organ transplant.
17. Patient has received prior radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior study treatment initiation.

Note: A 7-day washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to bone lesions.

18. Patient has any ongoing radiation-related toxicity or an ongoing corticosteroid requirement due to radiation.
19. Patient has an active or history of autoimmune disease or immune deficiency, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
 - a. Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
 - b. Patients with controlled type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

-
- c. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (eg, patients with psoriatic arthritis are excluded) are eligible for the study provided all of the following conditions are met:
- Rash must cover < 10% of body surface area.
 - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
 - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
20. Patient has medical conditions requiring chronic steroid therapy (ie, > 10 mg/day of prednisone or its equivalent) or anticipates the need for systemic immunosuppressive medications during treatment with study drug, with the following exceptions:
- a. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.
 - b. Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (eg, 48 hours of corticosteroids for a contrast allergy) are eligible.
 - c. Patients who received corticosteroids for chronic obstructive pulmonary disease or asthma or low-dose corticosteroids for orthostatic hypotension are eligible.
21. Patient has a history of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on Screening chest CT scan.
- Note: A history of radiation pneumonitis in the radiation field (fibrosis) is permitted as long as resolved/asymptomatic.
22. Patient has an uncontrolled infection requiring active antimicrobial treatment.
23. Patient has active tuberculosis.
24. Patient has received a live or live-attenuated vaccine within 4 weeks prior to the first dose of study treatment or anticipates the need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab.
- Note: Administration of killed vaccines and approved COVID-19 vaccines is allowed.
25. Patient has known active infection with HIV.

26. Patient has known infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), except for controlled active HBV or fully treated HCV infection, which are eligible and are defined as follows:
- a. For patients with active HBV, controlled disease is considered HBV DNA < 500 IU/mL during the Screening Period with willingness to continue antiviral treatment during the length of the trial. The patient must be on anti-HBV treatment (per local standard of care; eg, entecavir) for a minimum of 14 days prior to trial entry.
 - b. For patients with HCV, only cured disease or HCV considered fully treated and no longer requiring antiviral therapy for control is permitted.
 - c. Patients with co-infection with HCV and HBV, defined as HCV RNA positive and HBsAg positive, are not eligible; however, patients who are HCV Ab+ and HBV core antibody (HBcAb) positive but HBsAg- are not considered to have co-infection and are eligible.

27. Patient has inadequately controlled arterial hypertension (defined as systolic blood pressure [BP] ≥ 150 mmHg and/or diastolic BP ≥ 100 mmHg).

Note: Anti-hypertensive therapy to achieve eligibility criteria is permitted. If one session's BP reading is exclusionary, an average of 3 BP readings across 2 sessions can be used to meet eligibility.

28. Patient has a prior history of hypertensive crisis or hypertensive encephalopathy.
29. Patient has had significant vascular disease (eg, aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment.
30. Patient has had a history of hemoptysis (defined as ≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment.
31. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
32. Current or recent (within 10 days of first dose of study treatment) use of aspirin (≥ 325 mg/day) or treatment with dipyridamole, ticlopidine, clopidogrel, or cilostazol.
33. Chronic daily treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Note: Occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed.

34. Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purposes.

Note: Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an international normalized ratio (INR) $\leq 1.5 \times$ upper limit of normal (ULN) and activated partial thromboplastin time (aPTT) is within normal limits within 14 days prior to initiation of study treatment. For prophylactic use of anticoagulants or thrombolytic therapies, the approved dose as described by the local label may be used.

35. Patient has had a core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the first dose of bevacizumab.
36. Patient has had a history of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment.
37. Patient has had a history of intestinal obstruction and/or clinical signs or symptoms of GI obstruction including subocclusive disease related to the underlying disease or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months prior to initiation of study treatment.

Note: Patients with signs/symptoms of subocclusive syndrome/intestinal obstruction at time of initial diagnosis may be enrolled if they have received definitive (surgical) treatment for symptom resolution.

38. Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure.
39. Patient has a serious, nonhealing or dehiscing wound, active ulcer, or untreated bone fracture.
40. Patient has metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (≤ 30 mm from the carina) of large volume.

Note: Patients with vascular invasion of the portal or hepatic veins are eligible.

41. Patient has had a history of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including but not limited to peptic ulcer disease, diverticulitis, or colitis.
42. Patient has had another malignancy, other than those with negligible risk of death, including but not limited to nonmelanoma skin cancer, low-risk localized or cured prostate cancer, ductal carcinoma in situ, or carcinoma in situ of the cervix, within 2 years prior to Screening.
43. Patient has had a history of significant cardiovascular disease such as stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within 6 months prior to Screening.
44. Patient has known New York Heart Association congestive heart failure Grade $\geq$ II.
45. Patient has another unstable or severely uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the risk to the patient associated with his or her participation in the trial.

6. TRIAL PROCEDURES AND ASSESSMENTS

Time points for assessments to be collected throughout the study can be found in the following tables:

- [Table 1: Screening Assessments Checklist](#)
- [Table 2: Schedule of Assessments: CHS-388/Placebo + Atezolizumab + Bevacizumab, q3 week Dosing](#)
- [Table 3: Schedule of Pharmacokinetic and Anti-Drug Antibody Assessments: CHS-388/Placebo + Atezolizumab + Bevacizumab, q3 week Dosing](#)

A brief description of all assessments is presented in Section [6.1](#).

6.1. Procedures and Assessments

All potential patients will undergo Screening assessments to determine study eligibility. Patients who fail screening criteria may be rescreened later within the initial Screening Period (ie, ≤ 30 days from first dose) to confirm eligibility. If rescreening occurs after the initial Screening Period, sites should contact the Medical Monitor for approval. During the Screening Period, a patient number will be assigned.

6.1.1. Informed Consent

Patients potentially eligible for participation must sign an informed consent form (ICF) before initiating any study-specific procedures. Standard of care assessments that fulfill study eligibility requirements may be performed before patient signing the ICF.

6.1.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section [5.1](#) and Section [5.2](#), respectively) will be reviewed for each potential patient and documented in the patient medical record and electronic case report form (eCRF).

6.1.3. Medical History, Demographics, and Cancer History

Each patient's complete medical history will be obtained, including demographics, cancer history, and documentation of all previous treatments and treatment results (ie, best response). Disease characterization includes but is not limited to Child-Pugh score ([Appendix 3](#)) and BCLC stage ([Appendix 4](#)).

6.1.4. Prior/Concomitant Medications and Procedures

At Screening, concomitant and previous medications and procedures will be assessed including all medications/procedures that have occurred within the previous 30 days (previous 6 weeks for live attenuated vaccines). In addition, any cancer treatment procedures from any time in the past (eg, radiation, surgical resection) should be captured under prior procedures. Assessment of any change in concomitant medications or procedures since the last visit will occur at all patient visits through Safety Follow-up.

6.1.5. Physical Examination

A full physical examination will be performed at Screening and will include vital signs (temperature, blood pressure [sitting for 5 minutes], pulse rate, and respiratory rate), height, and weight, as well as a systematic physical examination; this will constitute the Baseline examination. If vital signs need to be repeated during a single visit, assessments should be conducted approximately 5 minutes apart. **Clinically significant findings at Screening should be recorded as medical history.**

Following Screening, physical examination will be symptom-directed and will include evaluation of disease-relevant systems and capture of vital signs. Patient weight should be taken predose on Day 1 of each cycle to calculate the appropriate doses of CHS-388/placebo and bevacizumab to be administered on that cycle. Alternatively, sites may follow their institutional practice of using the Cycle 1 Day 1 (C1D1) weight to dose throughout the study unless there is a > 5% change. While D1 physical examinations must be conducted in person or per institutional standards, physical examinations on all other visit days may be done by telemedicine following institutional procedures.

Results from the symptom-directed physical examinations will be used for assessment of disease response. Any new clinically significant abnormality from Baseline should be recorded as an AE.

If the physical examination at Screening is performed within 7 days of the first dose (C1D1), the Screening assessment can be used and does not need to be repeated. The symptom-directed physical examination should be done within a 48-hour window prior to dosing in all subsequent cycles.

6.1.6. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status will be assessed at Screening and serially during the study treatment period, as well as at the EoT Visit and 30-day Safety Follow-up Visit. If the ECOG performance status assessed at Screening is performed within 7 days of the first dose (C1D1), the Screening assessment can be used and does not need to be repeated. The ECOG performance status assessment should be done within a 48-hour window prior to dosing in all subsequent cycles. Refer to [Appendix 5](#) for a sample of the ECOG assessment.

6.1.7. Electrocardiogram

At Screening, a standard 12-lead electrocardiogram (ECG) will be conducted to determine a baseline following an approximate 10-minute rest period in all patients and will be interpreted by the Investigator to confirm eligibility. Subsequent ECGs will be obtained as clinically indicated.

6.1.8. Esophagogastroduodenoscopy

At Screening, an EGD must be performed unless the patient has undergone EGD within 6 months of study treatment initiation. All size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment.

6.1.9. Clinical Laboratory Tests

The following parameters will be measured as indicated at Screening ([Table 1](#)) and/or throughout the treatment period ([Table 2](#)) and will be analyzed locally.

- A serum β hCG pregnancy test should be collected at Screening and must be performed within 7 days before the first dose for all WCBP. Subsequent pregnancy tests during the treatment period may be either urine or serum.
- Blood chemistry laboratory parameters include albumin, total protein, sodium, potassium, calcium, phosphorous, chloride, bicarbonate (or carbon dioxide), blood urea nitrogen or urea, creatinine, lipase, amylase, magnesium, glucose, and lactate dehydrogenase. Liver function tests include serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, and alkaline phosphatase.
- Hematology laboratory parameters include hemoglobin, hematocrit, red blood cell count, platelet count, and white blood cell count with differential to include levels of neutrophils, lymphocytes, eosinophils, and monocytes.
- Fasting lipid panel includes total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglycerides.
- Coagulation laboratory parameters include aPTT and either prothrombin time (PT) or INR. For patients receiving anticoagulation therapy affecting PT, an INR must be obtained.
- Complete urinalysis with qualitative analysis for protein. Urinalysis parameters should include specific gravity, pH, glucose, protein, ketones, and blood.
- The levels of TSH and free T4 will be collected in all patients.
- AFP. Results do not have to be available to proceed with dosing.

Unscheduled assessments should be done as clinically indicated.

Clinically significant laboratory findings at Screening should be recorded as medical history.

Clinically significant laboratory findings identified after Screening, including but not limited to those findings resulting in a drug interruption/hold/reduction/discontinuation or medical intervention, should be reported as AEs (see Section [8.1.1](#) for the definition of an AE).

6.1.10. Additional Screening Laboratory Measurements

At Screening, the following assessments will be performed to determine eligibility:

Human immunodeficiency virus:

- Patients without documentation of a prior negative HIV test result (eg, antibody, antigen, or polymerase chain reaction-based test) are required to undergo HIV testing during Screening. Only patients with negative HIV results will be eligible to enroll.

Hepatitis:

- All patients will be tested for anti-HCV Ab and HBsAg at Screening. If Ab test is positive, hepatitis C RNA (viral load) or HBV DNA will be collected. Patients with a positive anti-HCV and HCV RNA titer or HBsAg test will be excluded from enrolling in the trial (except for patients with controlled viral disease as outlined in Section 5.2). While patients with HCV and HBV co-infection, defined as HCV RNA positive and HBsAg positive, are not eligible, patients who are HCV Ab+ and HBcAb+ but HBsAg- are not considered to have co-infection and are eligible.
- HCV viral load and HBV DNA will be assessed during the trial in patients who have a history of hepatitis C infection and hepatitis B infection, respectively. Serial monitoring should be conducted only in patients who have known disease.

6.1.11. Tumor Evaluation

Quantification of disease burden should be performed at Screening (Table 1) and as outlined in the Schedule of Assessments (Table 2) with liver CT or MRI (optimized for pre-contrast, arterial, and portal venous phase [eg, triphasic or other institutional HCC protocol adequate for mRECIST evaluation]) and contrast-enhanced CT or MRI of the chest, abdomen, and pelvis. Other scans may be performed (eg, brain MRI, bone scan) if clinically indicated or if the area is a site of known disease. The modality chosen to evaluate each individual patient should be the same throughout the duration of the study, when possible.

Assessment of response will be evaluated using RECIST v1.1 as well as mRECIST (Appendix 2) and clinical symptoms.

See Section 6.3 for more information on disease-specific tests to be performed at Screening and while on study.

6.1.12. Archival Tumor Tissue and Tumor Biopsies

Archival tumor tissue with associated pathology report collected within 18 months prior to enrollment is required to be collected, if available. Newly obtained core or excisional biopsy of a tumor lesion not previously irradiated is optional and preferred to archival tissue. Formalin-fixed paraffin embedded (FFPE) tissue blocks are preferred to slides. Tumor biopsies should be core, incisional, or excisional biopsies (not fine needle aspirates) of soft tissue (eg, LN, lung, liver, other soft tissue metastasis) or of the primary tumor.

Fresh tumor biopsies of accessible tumor tissue are strongly encouraged to aid in the evaluation of CHS-388/placebo tumor effect but are considered optional unless otherwise specified. If obtained, they will be performed at the time points outlined in Table 1 and Table 2. If a standard-of-care biopsy is performed while on trial (note: this is not required) and archived at the site, the Sponsor may request this on-trial archived tumor tissue with associated pathology or other tissue profiling reports.

Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut.

If tumor tissue is available, an FFPE tumor specimen or specimen in a paraffin block (preferred) or approximately 10 to 15 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks of randomization.

If FFPE tumor tissue specimens described above are not available, any type of FFPE specimens (including fine-needle aspiration, cell pellet specimens [eg, from pleural effusion or ascites], and lavage samples) are also acceptable. This specimen should be accompanied by the associated pathology report. If tumor tissue is not available (eg, depleted because of prior diagnostic testing), patients are still eligible.

Refer to the SRF388-201 Laboratory Manual for details on sample handling procedures and shipping requirements for fresh tumor biopsies and archival tumor tissue samples.

Archival tumor tissue and fresh tumor biopsy tissue samples may be analyzed at a central laboratory or a specialized laboratory vendor to assess the following:

- Potential predictive biomarkers in the tumor and tumor microenvironment
- In situ examination of markers on tumor cells, distinct immune cell populations, and other nontumor cellular compartments (eg, stroma) by immunohistochemistry may include but are not limited to: IL-27 pathway proteins, PD-L1, and T-cell and macrophage populations as assessed by various immune cell markers (eg, CD8 and CD68)
- Gene expression evaluation of tumor specific and immune-related genes and/or gene signatures

Samples collected during the study will be banked for up to 10 years. Any remaining material, as permitted, may be used to conduct research related to either CHS-388 and IL-27 relevant pathways, or to cancer biology in general.

6.1.13. Pharmacokinetic Sampling

PK sample collection time points are shown in [Table 3](#). Serum samples will be analyzed for CHS-388 and atezolizumab concentrations.

The date and time of each sample collection and the date and time of the prior study drug dose must be recorded for all collected samples.

An additional PK sample, beyond those listed in [Table 3](#) should be drawn at the time of any unusual safety event (ie, an AE different in type and severity from that which is expected in the setting of CHS-388, atezolizumab or bevacizumab use).

Refer to the SRF388-201 Laboratory Manual for details on sample handling procedures and shipping requirements for PK samples.

6.1.14. Biomarker Assessments

Samples will be collected for biomarker analysis to investigate the biological effects of CHS-388 at the molecular and cellular level, as well as to evaluate how changes in the markers and immune cell populations may relate to exposure and clinical outcomes. The goal of the biomarker assessments is to provide supportive data for the clinical trial. There may be circumstances when a decision is made to stop a collection, not perform, or discontinue an

analysis due to either practical or strategic reasons (eg, inadequate sample number, sample quality issues precluding analysis, etc.). Therefore, sample collection and/or analysis may be omitted at the discretion of the Sponsor. The timing around collection of these assessments is outlined in [Table 1](#) (archival tumor tissue) and [Table 2](#).

Additional biomarker samples, beyond those listed in [Table 2](#), may be requested (when feasible) at the time of any unusual safety event (ie, an AE different in type and severity from that which is expected in the setting of CHS-388, atezolizumab, or bevacizumab use).

The following biomarker samples may be analyzed at a central laboratory or a specialized laboratory vendor:

- Blood serum for EBI3
- Blood (whole blood and PBMCs) for immunophenotyping and immune monitoring:
 - To monitor the effects of treatment on various peripheral blood immune cell populations. Subsets may include, but are not limited to, monocytes, neutrophils, myeloid-derived suppressor cells, and T/NK/myeloid-cell populations.
- Blood serum for cytokine/chemokine/soluble factors:
 - For profiling of potential predictive and pharmacodynamic biomarkers of response and/or resistance to CHS-388.
 - Serum levels of soluble factors associated with cancer and immunological function will be assessed. Examples include but are not limited to: IL-27, MCP-1 (CCL2), TNF α , MIP-1 α (CCL3), MIP-1 β (CCL4), IL-1 β , IFN γ , IL-10, IL-8, IL-6, and IL-2.

Samples collected during the study will be banked for up to 10 years. Any remaining material, as permitted, may be used to conduct research related to either CHS-388 and IL-27 relevant pathways, or to cancer biology in general.

Refer to the SRF388-201 Laboratory Manual for biomarker sample handling procedures and shipping requirements.

6.1.15. Pharmacogenomics Assessment

A buccal swab will be collected from all patients for pharmacogenomics assessment at Screening ([Table 1](#)) or prior to dosing at C1D1 ([Table 2](#)). This sample may be used to study how polymorphisms in germline DNA affect PK and metabolism of CHS-388, as well as clinical response to CHS-388. This sample may also serve as a germline DNA control to help interpret sequencing and gene copy number variation data obtained from patient tumor samples.

Refer to the SRF388-201 Laboratory Manual for biomarker sample handling procedures and shipping requirements.

6.2. Safety Assessments

6.2.1. Adverse Events

SAEs will be immediately reported from the time of the signing of the ICF until the Long-term Follow-up Visit, 90 days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later, or until the patient has been deemed to be a screen failure. At any time after completion of the AE reporting period, if an Investigator becomes aware of an SAE that the Investigator considers to be related to any study drug, the event must be reported.

Nonserious AEs should be monitored from the time of completion of the initial Screening assessments through the Safety Follow-up Visit or 30 days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later. After the patient is enrolled, all AEs will be captured on the eCRF.

See Section 8.2 for a full description of the collection and reporting of AEs during this study.

6.2.2. Anti-Drug Antibody Assay

An ADA assay for CHS-388/placebo will be performed at a central laboratory for immunogenicity testing. Refer to the SRF388-201 Laboratory Manual for sample handling procedures and shipping requirements. The time points for the collection of this assessment are detailed in Table 3. An additional ADA sample, beyond those listed, may be requested (when feasible) at the time of any unusual safety event (ie, an AE different in type and severity from that which is expected in the setting of CHS-388, atezolizumab, or bevacizumab use). Patients who test positive for CHS-388 or atezolizumab ADA will be tested throughout the study or until the EoT visit.

6.3. Response Assessment Procedures

Response and progression will be determined by Investigator assessment at the time points shown in Table 2 as compared to Baseline tumor imaging (see Section 6.1.11) performed in Screening Assessments (Table 1). The modality chosen to evaluate each individual patient should be the same throughout the duration of the study. Redacted images may be collected.

For patients who experience an objective response or who progress on therapy and continue treatment past progression, confirmatory scans should be done a minimum of 4 weeks and a maximum of 9 weeks later. Patients will be expected to continue to follow the response assessment schedule as outlined in the Schedule of Assessments (Table 2).

These evaluations will be conducted on treatment or following treatment discontinuation until the patient experiences PD or discontinues the study. See Section 6.3.1 for more information regarding response procedures and response criteria.

Note that pseudoprogression or delayed response may occur in patients treated with immune-modulating agents such as CHS-388 and atezolizumab, and therefore patients may continue on treatment past progression if the patient is willing and the treating Investigator agrees the patient is deriving clinical benefit and is not increasingly symptomatic.

6.3.1. Response Evaluation Criteria

All disease-specific assessments are to be completed at the time points outlined in the Schedule of Assessments (Table 2). The modality chosen to evaluate each individual patient should be the same throughout the duration of the study.

RECIST v1.1 and HCC mRECIST (Appendix 2)^{45, 46} will be applied at the time points specified in Table 2. RECIST v1.1 is the primary method of outcomes assessment. HCC mRECIST outcomes are secondary.

At a minimum, assessments include a liver CT or MRI (optimized for pre-contrast, arterial, and portal venous phase [eg, triphasic or other institutional HCC protocol adequate for HCC mRECIST evaluation]) and contrast-enhanced CT or MRI of the chest, abdomen, and pelvis. Other scans may be performed (eg, brain MRI, bone scan) if clinically indicated or if the area is a site of known disease. The MRI may be substituted if clinically indicated, but the modality chosen to evaluate each site of disease for an individual patient should be the same throughout the duration of the study. The frequency outlined is the minimum required for study participation. Imaging will also be performed at the end of treatment if the patient is discontinued for reasons other than disease progression and a previous assessment has not been performed within 30 days.

Patients may continue on treatment past progression if deemed clinically appropriate (see Section 4.6) and safe by the Investigator. Patients who remain on study past progression should have a confirmatory scan after at least 4 weeks but not more than 9 weeks later.

Local assessment of objective response will be evaluated using RECIST 1.1 and HCC mRECIST, as well as clinical decision making. Please refer to Table 31 (RECIST 1.1 Lesion Response Criteria) and Table 32 (Evaluation of Overall Response by RECIST 1.1). For HCC mRECIST criteria, please refer to Table 33. The Sponsor may collect copies of the patient images of all disease-specific assessments obtained on study for sponsor and/or independent radiology review.

6.4. Safety Follow-up Visit

All patients will have a Safety Follow-up Visit at 30 days (+ 5 days) as well as a Long-term Follow-up Visit at 90 (+ 5) days after the last dose of study drug (CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later). If possible, this visit should occur before the initiation of any subsequent anticancer therapy. Patients continuing to experience toxicity at this point following the discontinuation of treatment will continue to be followed at least monthly until resolution or determination in the clinical judgment of the Investigator that no further improvement is expected. A Safety Follow-up Visit is not required for patients who discontinue all study drugs due to a treatment interruption of CHS-388/placebo and bevacizumab lasting > 42 days and atezolizumab lasting > 12 weeks. However, these patients must complete the Long-term Follow-up Visit and will be followed for survival.

6.5. Long-term Follow-up for Safety

SAEs will be reported through 90 (+ 5) days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later. Pregnancy events will be followed for 90 days

after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later. Long-term follow-up reporting may be conducted in person or by phone.

6.6. Survival Follow-up

All patients will be followed for survival every 6 months for 4 years from randomization. This assessment can be conducted by telephone interview or medical chart review. Information on initiation of other anticancer therapy, including start date, therapy type, and response on treatment, will be collected.

6.7. Concomitant Medications or Procedures

6.7.1. Transfusion Support (Prophylaxis or Supportive Care)

Blood cell transfusions (packed red blood cells or platelets) are permitted as clinically indicated. Note that transfusion for the purpose of enabling a patient to meet inclusion criteria is not permitted.

6.7.2. Prohibited Medications

Additional Anticancer Therapy, Other Investigational Agents, and Immunotherapy

During the study treatment period, patients are not to receive any additional anticancer therapy, other investigational agents, or immunotherapy not specified in this protocol. If the Investigator determines that a participant requires any of these treatments for any reason, all study interventions must be discontinued.

Herbal Therapies

Concomitant use of herbal therapies/traditional Chinese medicine with anti-cancer activity included in the product label is prohibited.

Corticosteroids

Corticosteroids used as an anticancer therapy (eg, > 10 mg/day prednisone or equivalent) are not permitted; however, they are allowed as a premedication, as physiologic replacement, or for symptomatic management (see also Section 6.7.3).

- Systemic corticosteroids are permitted for the following purposes:
 - To modulate symptoms of an AE that is suspected to have an immunologic etiology
 - As needed for the prevention of emesis
 - Premedication for IV contrast allergies
- In addition, the following glucocorticoid use is allowed:
 - For topical use or ocular use
 - Intraarticular joint use
 - For inhalation in the management of asthma or chronic obstructive pulmonary disease

Note: Inhaled steroids are allowed for the management of asthma.

Systemic Immunostimulatory Agents

Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited during treatment with atezolizumab because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

Systemic Immunosuppressive Medications

Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during treatment with atezolizumab because these agents could potentially alter the efficacy and safety of atezolizumab.

Anticoagulants

Use of full-dose anticoagulants, thrombolytic therapy at therapeutic doses, or antiplatelet therapy is prohibited, with the following exceptions:

- Local label-recommended doses of anticoagulants or thrombolytic therapies for prophylactic use are permitted.
- Low-dose aspirin (< 325 mg/day) is permitted. Co-administration of proton pump inhibitors is strongly recommended to reduce potential GI damage.
- If a patient experiences a venous thromboembolism event while still receiving study drug, it may still be possible for the patient to remain on study drug despite anticoagulation treatment, depending on the grade (see Section 7.5).
- The preferred choice for anticoagulation treatment should be low molecular weight heparin (LMWH) per American Society of Clinical Oncology guidelines.⁴⁷ Warfarin or Coumadin®-like products are not allowed.

Use of warfarin or Coumadin-like products for any reason, including for prophylactic use, is prohibited.

- Prophylactic use of low-dose anticoagulation, unfractionated heparin, or LMWH is permitted.

NSAIDs

Concomitant chronic use of NSAIDs while receiving study drugs is prohibited, with the exception of chronic low-dose aspirin (< 325 mg/day). However, for the symptomatic relief of medical conditions (eg, headache, fever), intermittent or short-term intake of oral NSAIDs is allowed when co-administered with proton pump inhibitors to reduce potential GI damage.

Vaccines

Live, attenuated vaccines (eg, FluMist®) are prohibited during treatment with atezolizumab and for 5 months after the last dose of atezolizumab. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from study intervention or vaccination may be required. The Investigator is to discuss prohibited medication/vaccination with the Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the participant's primary physician.

- Exception: The Sponsor is supportive of patients receiving a Health Authority-approved COVID-19 vaccine if they have no known contraindications to the vaccination. If administered, the name of the vaccine, the dose, and the dates administered should be documented in the medical records as well as the concomitant medication section of the eCRF. Investigators should have an informed risk/benefit discussion with the patient in making the decision to receive the vaccine and monitor for toxicity as there could be unknown risks of (1) heightened immune response and thus toxicity or (2) diminished immune response to either the study treatment, the vaccine, or both. If a trial patient decides to pursue an approved COVID-19 vaccination, the Sponsor recommends scheduling vaccination such that the full vaccination course occurs at least 2 weeks before C1D1, when possible.

6.7.3. Cautionary Therapies

Herbal therapies are cautionary therapies and are not recommended because their PK profiles, safety profiles, and drug-drug-interaction potential are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used at the discretion of the Investigator.

Additionally, systemic corticosteroids and TNF α inhibitors may attenuate potentially beneficial immunologic effects of atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF α inhibitors would be routinely administered, alternatives (eg, antihistamines) should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF α inhibitors may be administered at the discretion of the Investigator with Sponsor approval.

6.7.4. Other Concomitant Therapies or Procedures

Radiation therapy to a symptomatic or progressing solitary lesion including the brain may be allowed at the Sponsor's discretion and if the Investigator feels the patient is deriving clinical benefit/disease control in the other disease sites.

Any other medication, which is considered necessary for the patient's welfare, including antimicrobial prophylaxis and growth factor support, and which is not expected to interfere with the evaluation of the study drugs, may be given at the discretion of the Investigator.

Supportive care medicines (eg, bisphosphonates or RANK ligand inhibitors) are allowed on trial.

Patients with active hepatitis B should be treated with appropriate anti-viral medications as per the local standard of care.

Patients may receive a COVID-19 vaccination. Because COVID-19 vaccines are reported to have side effects similar to those of an CCI, the vaccination should take place at a different place and time from any trial CCI. For vaccines requiring 2 doses, both doses should be administered in this fashion. For any patient presenting to clinic or emergency department with symptoms consistent with COVID-19 infection,⁴⁸ testing for the presence of the novel coronavirus is recommended, as well as isolation and quarantine following institutional and local health authority guidance⁴⁹ (for experience and recommendations specific to oncology clinics). AEs or treatment discontinuation suspected to be attributable to infection with COVID-19 should be indicated as such on the relevant case report forms.

6.7.5. Contraception and Pregnancy

The effects of the study treatment on conception, pregnancy, and lactation are unknown.

At Screening, all male and female patients who are not surgically sterile or postmenopausal must agree to use medically acceptable methods of birth control for the duration of treatment with study drug and for 6 months after the last dose of any study drug. Male patients must refrain from donating sperm during this period.

- A male patient is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.
- A female patient is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.
 - Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly effective contraception is defined as use of one or more methods that result in a low failure rate (ie, < 1%). Highly effective contraceptive measures include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable.
- Intrauterine device.
- Intrauterine hormone-releasing system in combination with a barrier method (preferably male condom).
- Surgical sterilization.
 - Male patient is vasectomized (with documented medical confirmation of surgical success) and is the sole sexual partner of a WCBP.
 - Female patient has undergone bilateral tubal ligation.
- Complete sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Sexually active men, and women using contraceptive methods described above, should also use barrier contraception with spermicide. Acceptable barrier forms of contraception are condoms or diaphragm.

Azoospermic male patients and WCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, female patients must still undergo pregnancy testing as described in the Schedule of Assessments ([Table 1](#) and [Table 2](#)).

The use of birth control methods is also not required if the male partner (of the female patient) has a documented history of a vasectomy or if the female partner (of the male patient) has a documented history of bilateral oophorectomy, hysterectomy, tubal ligation, or if she is > 55 years of age and postmenopausal for at least 1 year.

7. STUDY DRUG MATERIALS AND MANAGEMENT

The following study drugs will be used in this trial:

- CHS-388 [REDACTED] mg/kg [REDACTED] or CHS-388 placebo [REDACTED]
- Atezolizumab [REDACTED] mg [REDACTED]
- Bevacizumab [REDACTED] mg/kg [REDACTED]

Patients will receive CHS-388/placebo, atezolizumab, and bevacizumab q3 weeks on Day 1 of a 21-day cycle. Patients in the Safety Lead-In will receive open-label CHS-388 (not placebo) with atezolizumab + bevacizumab. All [REDACTED] should be administered under the supervision of a physician, or other trial personnel, experienced in the use of [REDACTED] agents. The order and timing of study drug administration are presented in Table 9.

Table 9: Order and Timing of Study Drug Administration in Trial SRF388-201

Dose, Route, and Regimen (Study Drugs Listed in Order of Administration)	[REDACTED] Details
CHS-388 [REDACTED] mg/kg [REDACTED] OR placebo [REDACTED] on Day 1 ^a	Suggested [REDACTED] duration range: Approximately 20 to 60 minutes There should be a 30-minute observation period between the end of the CHS-388/placebo [REDACTED] and the start of the atezolizumab [REDACTED] ^b
Atezolizumab [REDACTED] mg [REDACTED] on Day 1 ^a	[REDACTED] 60 (± 15) minutes for the first [REDACTED] [REDACTED] 30 (± 10) minutes for subsequent [REDACTED] [REDACTED] if tolerated ^b There should be a minimum of 5 minutes between the end of the atezolizumab [REDACTED] and the start of the bevacizumab [REDACTED]
Bevacizumab [REDACTED] mg/kg [REDACTED] on Day 1 ^a	[REDACTED] 90 (± 15) minutes for the first [REDACTED] [REDACTED] 60 (± 10) minutes for the second [REDACTED] [REDACTED] 30 (± 10) minutes for subsequent [REDACTED] [REDACTED] if tolerated ^c

Abbreviations: [REDACTED]; [REDACTED]

^a All study drugs are administered on Day 1 of a 21-day cycle.

^b Atezolizumab should be [REDACTED] 30 (± 10) minutes if the previous [REDACTED] was tolerated without an [REDACTED] or 60 (± 15) minutes if the patient experienced an [REDACTED] with the previous [REDACTED]

^c Bevacizumab should be [REDACTED] 60 (± 10) minutes if the previous [REDACTED] was tolerated without an [REDACTED] or 90 (± 15) minutes if the patient experienced an [REDACTED] with the previous [REDACTED]. If the 60-minute [REDACTED] was well tolerated, bevacizumab may be [REDACTED] 30 (± 10) minutes thereafter.

Patients will receive CHS-388/placebo, atezolizumab, and bevacizumab q3 weeks until documented PD or unacceptable toxicity through C35. Doses of CHS-388/placebo, atezolizumab, and/or bevacizumab may be administered within a ± 3-day window; otherwise, they should be skipped for that cycle.

CHS-388/placebo, atezolizumab, and bevacizumab dose holds and modifications are described in Section 7.2 and Section 7.5. If an AE is thought to be due to 1 study drug and unrelated to the others (or due to 2 study drugs and unrelated to the third), the patient may continue to receive 1 or both of the other study drugs while holding or discontinuing the toxic agent(s).

7.1. CHS-388/Placebo

7.1.1. Description of CHS-388

CHS-388 drug product is a CCI into a CCI and sealed with a CCI and stored at -20°C. The Good Manufacturing Practice drug product contains CCI for CCI. All lots of drug product are tested to ensure product identity, strength, quality, purity, and potency. CCI Additional details on the preparation and administration of CHS-388 drug product will be provided to the Investigator/Pharmacist in the SRF388-201 Pharmacy Manual.

7.1.2. Description of Placebo

Placebo is CCI, United States Pharmacopeia) in an CCI bag. Sites will deliver an CCI in the same manner that they would CCI CHS-388 CCI. Additional details on the preparation and administration of placebo will be provided to the Investigator in the SRF388-201 Pharmacy Manual.

7.1.3. CHS-388/Placebo Blinding

Each site will designate an unblinded pharmacist to use a double-blind technique. The CCI and CHS-388 CCI will be indistinguishable. The unblinded pharmacist will employ the same institutional standard CCI meeting the material recommendations in the SRF388-201 Pharmacy Manual. The patient, the Investigator, the site CCI personnel, and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the patients will be unaware of the group assignment.

See Section 4.5 for a description of the method of unblinding a patient during the trial, should such action be warranted.

7.1.4. CHS-388 Dosage

CHS-388 is administered as an CCI supplied by the Sponsor at a dose of CCI mg/kg body weight. Dose reductions and discontinuations for CHS-388 in individual patients may be made based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor (see Section 7.2).

7.1.5. CHS-388/Placebo Administration

CHS-388/Placebo will be administered as an CCI. Please see Table 9 for additional details regarding the order and timing of study drug administration. Refer to the SRF388-201 Pharmacy Manual for detailed administration instructions.

7.1.5.1. CHS-388/Placebo CCI Medications

For the first administration of CHS-388/placebo (C1D1), no CCI medication is required. If a Grade ≥ 1 CCI-related AE is recorded at any dose, then for all subsequent doses for that patient, the following premedications should be administered:

- Antipyretics (oral acetaminophen 650 to 1000 mg)
- Antihistamine (oral or IV diphenhydramine 25 to 50 mg or equivalent)

Patients with a Grade ≥ 2 CCI should also be premedicated with a glucocorticoid (IV 20 mg dexamethasone or 80 mg methylprednisolone) for all subsequent CCI

7.1.5.2. CHS-388/Placebo CCI Medications

No specific CCI medications are required for CHS-388/placebo.

7.1.6. CHS-388 Storage

CHS-388 is supplied in a CCI containing at least CCI mL at a target concentration of CCI for CCI. The drug product CCI should always be stored in the container provided to the pharmacy and should be stored at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ (-13°F to 5°F) protected from light. Caution is required when handling CHS-388. Pharmacists should follow standard procedures for the handling of investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, the individual should treat for physical exposure (skin washing) or inhalation (move to fresh air, as necessary), and, if needed, seek medical advice.

7.2. CHS-388/Placebo Dose Holds and Modifications

Patients will be monitored continuously for toxicity while on study drug. Toxicity severity will be assessed using the NCI-CTCAE version 5.0 or higher. Every effort should be made to administer study drug according to the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of study drug may need to be adjusted as described below.

7.2.1. CHS-388/Placebo Dose Holds, Modifications, and Discontinuation

Hematologic toxicities that are not clearly related to disease progression, intercurrent illness, or concomitant medications should be managed according to the guidelines in Table 10. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

Table 10: Hematologic Toxicities Attributed to CHS-388 Leading to Dose Hold, Dose Modification, or Discontinuation of CHS-388/Placebo

Toxicity	Recommended Dose Delay or Reduction
Neutropenia	
Grade 3 (ANC < 1000/ μ L; 1×10^9 /L) with a single temperature of > 38.3°C (101°F) or a sustained temperature of $\geq 38^\circ\text{C}$ (100.4 °F) for > 1 hour	Hold until toxicity recovers to Baseline and then resume at reduced dose. If Grade ≥ 3 recurs, permanently discontinue.
Grade 4 (ANC < 500/ μ L; < 0.5×10^9 /L) persisting for ≥ 7 days, and/or complicated by infection	Permanently discontinue.
Grade 4 life-threatening consequences; urgent intervention indicated	Permanently discontinue.
Platelets	
Grade 3 (platelets < 50,000-25,000/ μ L; < 50.0 - 25.0×10^9 /L) with associated clinically significant bleeding	Permanently discontinue.
Grade 4 (platelets < 25,000/ μ L; < 25.0×10^9 /L) of any duration bleeding	Permanently discontinue.
Anemia	
Grade 4 anemia defined as life-threatening consequences; urgent intervention indicated (any duration)	Permanently discontinue.
All other hematologic toxicity	
Intolerable or recurrent Grade 2	Hold until resolves to baseline and resume at reduced dose.
Grade 3	Hold until resolves to baseline and resume at reduced dose.
Recurrent Grade 3 or 4	Permanently discontinue.
Grade 4 not detailed above	Permanently discontinue.

Abbreviation: ANC = absolute neutrophil count.

Steroids may be used to manage severe (Grade ≥ 3) hematologic toxicity if thought to be immune-related. All attempts should be made to rule out other causes such as metastases, sepsis, and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, lactate dehydrogenase, haptoglobin, bone marrow biopsy, or Coomb's test, etc., should be considered to confirm the diagnosis. The AE should be reported to the Sponsor regardless of etiology.

In the unlikely event of severe bone marrow suppression, a bone marrow biopsy should be performed, if clinically feasible, to assist in determining causality.

Nonhematologic toxicities that occur during treatment with CHS-388/placebo that are not clearly related to disease progression, intercurrent illness, or concomitant medications, should be managed according to the guidelines in [Table 11](#).

Table 11: Nonhematologic Toxicities Leading to Dose Hold, Modification, or Discontinuation of CHS-388/Placebo

Toxicity	Recommended dose delay or reduction
Hepatotoxicity	
Grade 2 AST/ALT: $> 3.0\text{-}5.0 \times \text{ULN}$ if Baseline was normal; $> 3.0\text{-}5.0 \times \text{Baseline}$ if Baseline was abnormal OR Total bilirubin: $> 1.5\text{-}3.0 \times \text{ULN}$ if Baseline was normal; $> 1.5\text{-}3.0 \times \text{Baseline}$ if Baseline was abnormal	Withhold until Grade ≤ 1 .
Grade 3 AST/ALT $> 5.0\text{-}20.0 \times \text{ULN}$ if Baseline was normal; $> 5.0\text{-}20.0 \times \text{Baseline}$ if Baseline was abnormal OR Total bilirubin: $> 3.0\text{-}10.0 \times \text{ULN}$ if Baseline was normal; $> 3.0\text{-}10.0 \times \text{Baseline}$ if Baseline was abnormal	Withhold until Grade ≤ 1 .
$> 2 \times \text{ULN}$ total bilirubin AND Grade ≥ 2 ALT/AST ($> 3 \times \text{ULN}$) in patients who enroll with Grade ≤ 1 ALT/AST OR $> 2 \times \text{ULN}$ total bilirubin AND doubling of ALT/AST in patients who enroll with Grade 2 ALT/AST	In the absence of biliary obstruction or other cause responsible for the concurrent elevation, permanently discontinue CHS-388/placebo.
Grade 4 ALT/AST elevation OR Grade 4 total bilirubin elevation	Permanently discontinue CHS-388/placebo.
Metabolic	
Grade 3 electrolyte disturbance	Hold CHS-388/placebo until resolves to Grade ≤ 1 or Baseline and resume with same dose (first occurrence) or with reduced dose after resolution (second occurrence).
Grade 4 electrolyte disturbance	Hold CHS-388/placebo until resolves to Grade ≤ 1 or Baseline and resume with same dose if resolves in ≤ 72 hours; permanently discontinue if resolution takes > 72 hours.

Toxicity	Recommended dose delay or reduction
Gastrointestinal	
Grade 3 nausea, vomiting, diarrhea	Hold CHS-388/placebo until resolves to Grade ≤ 1 or Baseline and resume with same dose if resolves in ≤ 72 hours with supportive care. If it lasts > 72 hours despite optimal supportive care, resume with reduced dose. Patients must be contacted by the Investigator or trial nurse daily until it is clear that the problem has resolved or requires additional support (eg, hospitalization).
Grade 4 vomiting or diarrhea	Permanently discontinue CHS-388/placebo.
Pneumonitis, colitis, or nephritis	
Grade 2	Hold CHS-388/placebo until resolves to Grade ≤ 1 and no longer requiring corticosteroids. If recurs at Grade ≥ 2 , permanently discontinue CHS-388/placebo.
Grade 3-4	Permanently discontinue CHS-388/placebo.
Skin toxicity	
Grade 3	Hold CHS-388/placebo until resolves to Grade ≤ 1 and no longer requiring corticosteroids. If recurs at Grade ≥ 2 , permanently discontinue CHS-388/placebo.
Grade 4	Permanently discontinue CHS-388/placebo.
CCI	
Grade 4	Permanently discontinue CHS-388/placebo.
Endocrinopathies (eg, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus)	
Grade 3 or 4	Withhold dose until resolved or clinically stable on hormone replacement therapy.
Other nonhematologic toxicities	
Grade 2 or 3 AE that, in the opinion of the Investigator, requires dose reduction	Hold CHS-388/placebo until resolves to Grade ≤ 1 or Baseline and resume at reduced dose. Evaluate at least once weekly following the initial identification of the toxicity until its resolution or stabilization.
Grade 4 ^a AE	Hold CHS-388/placebo until resolves to Grade ≤ 1 or Baseline and resume at reduced dose. Exception: asymptomatic amylase/lipase elevation of any duration.

Toxicity	Recommended dose delay or reduction
Recurrent Grade 3 or 4 AE	Permanently discontinue CHS-388/placebo.
Inability to taper corticosteroid < 10 mg per day prednisone or equivalent for > 42 days after last dose of CHS-388/placebo	Permanently discontinue CHS-388/placebo.
Treatment delays > 42 days because of study drug-related toxicities	Permanently discontinue CHS-388/placebo.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase;

CCI; ULN = upper limit of normal.

^a Other than laboratory abnormalities that Investigator deems clinically insignificant and that last ≤ 48 hours.

For all other toxicities, the Investigator may resume CHS-388/placebo treatment at the same dose level upon recovery of the toxicity to Grade ≤ 1 or Baseline value.

Dose reduction for CHS-388/placebo is described in Table 12.

Table 12: Dose Reduction for CHS-388/Placebo in Trial SRF388-201

	Initial dose	Dose reduction
CHS-388/Placebo	CCI mg/kg	CCI mg/kg

Any patient who requires > 1 dose-level reduction or requires holding of CHS-388/placebo for > 42 days will be permanently discontinued from CHS-388/placebo.

Patients who have a dose reduction because of a toxicity may not re-escalate the dose.

CCI

For CCI of any grade/severity, immediately interrupt the CHS-388/placebo CCI and manage symptoms. Management of CCI may require reduction in the CCI, or treatment discontinuation of CHS-388/placebo as outlined below:

- Grade 1 to 2 (mild or moderate): Once reaction symptoms resolve, resume the CCI at which the reaction occurred. If the patient does not experience any further reaction symptoms, CCI may resume at increments and intervals as clinically appropriate up to the CCI.
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the CCI at which the reaction occurred. Permanently discontinue CHS-388/placebo upon the second occurrence of a Grade ≥ 3 CCI.
- Grade 4 (life threatening): Permanently discontinue CHS-388/placebo.

No dose reductions of CHS-388/placebo for CCI are recommended.

For any patient who has a Grade ≥ 2 CCI with CHS-388/placebo, steroidal premedication should be used for all subsequent CCI (see Section 7.1.5.1).

7.3. Atezolizumab

7.3.1. Description of Atezolizumab

Atezolizumab drug product will be supplied by the Sponsor as a sterile CCI in a CCI -mL CCI. The CCI contains approximately CCI mL (CCI mg) of atezolizumab solution.

Refer to the SRF388-201 Pharmacy Manual and the atezolizumab Investigator's Brochure for information on the formulation and handling of atezolizumab.

7.3.2. Atezolizumab Dosage

Atezolizumab will be administered by CCI at a fixed dose of CCI mg on Day 1 of each 21-day cycle.

7.3.3. Atezolizumab Administration

Please see Table 9 for details regarding the order and timing of study drug administration and Table 13 for additional instructions regarding administration of first and subsequent atezolizumab CCI.

For detailed instructions on atezolizumab preparation, storage, and administration, refer to the SRF388-201 Pharmacy Manual. Guidelines for the medical management of CCI are provided in Table 21 and the atezolizumab Investigator's Brochure.

Table 13: Administration Instructions for First and Subsequent Atezolizumab CCI

First CCI	Subsequent CCI
- No premedication is permitted. - If clinically indicated, vital signs should be measured every 15 ($\pm$ 5) minutes during the CCI and at 30 ($\pm$ 10) minutes after the CCI. - Patients should be informed about the possibility of delayed CCI symptoms and instructed to contact their trial physician if they develop such symptoms.	- If the patient experienced an CCI with any previous CCI premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the Investigator. - Vital signs should be measured within 60 minutes prior to the CCI if the patient experienced an CCI with any previous CCI. - If the patient experienced an CCI with the previous CCI or if clinically indicated, vital signs should be measured during the CCI and at 30 ($\pm$ 10) minutes after the CCI.

Abbreviation: CCI

7.4. Bevacizumab

7.4.1. Description of Bevacizumab

Bevacizumab drug product will be supplied by the Sponsor as a CCI in single-use CCI-mg and CCI-mg preservative-free CCI to deliver mL or CCI mL of bevacizumab (CCI mg/mL). The CCI contains approximately mL or CCI mL of bevacizumab solution.

For information on the formulation and handling of bevacizumab, see the SRF388-201 Pharmacy Manual and the bevacizumab Investigator's Brochure.

7.4.2. Bevacizumab Dosage

Bevacizumab will be administered by CCI at a fixed dose of CCI mg/kg on Day 1 of each 21-day cycle.

7.4.3. Bevacizumab Administration

Please see Table 9 for details regarding the order and timing of study drug administration. Please see Table 14 for additional instructions regarding administration of first and subsequent bevacizumab CCI. Guidelines for the medical management of CCI are provided in Table 29.

Table 14: Administration Instructions for First and Subsequent Bevacizumab CCI

First CCI	Subsequent CCI
- No premedication is permitted prior to the bevacizumab CCI. - Vital signs should be at the end of CCI and 2 (± 1) hours after the CCI. - Patients should be informed about the possibility of delayed CCI symptoms and instructed to contact their trial physician if they develop such symptoms.	- If the patient experienced an CCI with any previous CCI, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the Investigator. - Vital signs should be recorded within 60 minutes prior to the CCI if the patient experienced an CCI with any previous CCI. - Vital signs should be recorded at the end of CCI and 2 (± 1) hours after the CCI if the patient experienced an CCI with any previous CCI.

Abbreviation: CCI.

7.5. Atezolizumab/Bevacizumab Dose Holds and Modifications

7.5.1. Atezolizumab/Bevacizumab Dose Holds, Modifications, and Discontinuation

No dose modifications for atezolizumab or bevacizumab are allowed.

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study drug. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab.

Bevacizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study drug. If the event resolves to Grade ≤ 1 , bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for > 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab.

Atezolizumab or bevacizumab treatment may be suspended for reasons other than toxicity (eg, surgical procedures) with Medical Monitor approval. The Investigator and the Medical Monitor will determine the acceptable length of treatment interruption, but it must be within 42 days for bevacizumab and within 12 weeks for atezolizumab.

If any study drug is withheld or discontinued, the other study drug(s) can be continued as long as the patient is experiencing clinical benefit, as determined by the Investigator per medical judgment.

Guidelines for the management of patients who experience specific AEs are provided in Section 7.5.1.1 and Section 7.5.1.2 and in the atezolizumab and bevacizumab Investigator's Brochures. For cases in which management guidelines are not covered in this protocol or in the atezolizumab or bevacizumab Investigator's Brochures, patients should be managed as deemed appropriate by the Investigator according to best medical judgment and institutional protocols.

7.5.1.1. Management of Adverse Events Associated With Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The Investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the trial and will also have CT scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in [Table 15](#).

Table 15: Management Guidelines for Pulmonary Events Associated With Atezolizumab, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	- Continue atezolizumab and monitor closely. - Re-evaluate on serial imaging. - Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c - For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	- Permanently discontinue atezolizumab and contact Medical Monitor.^c - Bronchoscopy or bronchoscopic alveolar lavage is recommended. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. The specific management guidelines for hepatic events are provided in [Table 16](#).

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated liver function tests, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 16: Management Guidelines for Hepatic Events Associated With Atezolizumab

Event	Management
Hepatic event, Grade 1	- Continue atezolizumab. - Monitor LFTs until values resolve to within normal limits or to Baseline values.
Hepatic event, Grade 2	All events - Monitor LFTs more frequently until return to Baseline values. Events of > 5 days' duration: - Withhold atezolizumab for up to 12 weeks after event onset.^a - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Hepatic event, Grade 3 or 4	- Permanently discontinue atezolizumab and contact Medical Monitor.^c - Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Abbreviation: LFT = liver function test.

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Gastrointestinal Events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in [Table 17](#).

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (eg, increased C-reactive protein, platelet count, or bandemia): perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 17: Management Guidelines for Gastrointestinal Events Associated With Atezolizumab

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.^c • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Abbreviations: GI = gastrointestinal; IV = intravenous(ly).

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Endocrine Events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in [Table 18](#).

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. TSH and T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (eg, TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotrophic hormone [ACTH] levels, and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 18: Management Guidelines for Endocrine Events Associated With Atezolizumab

Event	Management
Asymptomatic hypothyroidism	- Continue atezolizumab. - Initiate treatment with thyroid replacement hormone. - Monitor TSH weekly.
Symptomatic hypothyroidism	- Withhold atezolizumab. - Initiate treatment with thyroid replacement hormone. - Monitor TSH weekly. - Consider patient referral to endocrinologist. - Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH $\geq$ 0.1 mU/L and $<$ 0.5 mU/L: - Continue atezolizumab. - Monitor TSH every 4 weeks. TSH $<$ 0.1 mU/L: - Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	- Withhold atezolizumab. - Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. - Consider patient referral to endocrinologist. - Resume atezolizumab when symptoms are controlled and thyroid function is improving. - Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.^a
Symptomatic adrenal insufficiency, Grade 2-4	- Withhold atezolizumab for up to 12 weeks after event onset.^b - Refer patient to endocrinologist. - Perform appropriate imaging. - Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.^c - If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^a
Hyperglycemia, Grade 1 or 2	- Continue atezolizumab. - Initiate treatment with insulin if needed. - Monitor for glucose control.

Event	Management
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset.^b • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab.^c • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^a • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.^a • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

Abbreviations: IV = intravenous(ly); MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

^a Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

^b Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^c If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

Ocular Events

An ophthalmologist should evaluate visual complaints (eg, uveitis, retinal events). Management guidelines for ocular events are provided in [Table 19](#).

Table 19: Management Guidelines for Ocular Events Associated With Atezolizumab

Event	Management
Ocular event, Grade 1	- Continue atezolizumab. - Patient referral to ophthalmologist is strongly recommended. - Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. - If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Patient referral to ophthalmologist is strongly recommended. - Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Ocular event, Grade 3 or 4	- Permanently discontinue atezolizumab and contact Medical Monitor.^c - Refer patient to ophthalmologist. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Immune-Mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (eg, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, eg, in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated. Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 20](#).

Table 20: Management Guidelines for Immune-Mediated Myocarditis Associated With Atezolizumab

Event	Management
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset^a and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.^a • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c

Event	Management
Immune-mediated myocarditis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor.^c • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.^{a,b} • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Abbreviations: ECMO = extracorporeal membrane oxygenation; IV = intravenous(ly); VAD = ventricular assist device.

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

CCI and Cytokine Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an CCI of cytokine release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (eg, acetaminophen) for subsequent CCI. **Metamizole (dipyrone) is prohibited in treating atezolizumab-associated CCI because of its potential for causing agranulocytosis.**

CCI are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation of or engagement of endogenous or CCI T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction.⁵⁰ CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1,^{51, 52} including atezolizumab.

There may be significant overlap in signs and symptoms of CCI and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of CCI and CRS are provided in Table 21.

Severe COVID-19 appears to be associated with a CRS involving the CCI IL-6, IL-10, IL-2, and IFN γ .⁵³ If a patient develops suspected CRS during the trial, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per Investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table 21: Management Guidelines for CCI and Cytokine Release Syndrome Associated With Atezolizumab

Event	Management
<u>Grade 1^a</u> Fever^b with or without constitutional symptoms	- Immediately interrupt CCI - Upon symptom resolution, wait for 30 minutes and then restart CCI being given at the time of event onset. - If the CCI is tolerated at the CCI, the CCI. - If symptoms recur, discontinue CCI of this dose. - Administer symptomatic treatment,^c including maintenance of IV fluids for hydration. - In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. - For subsequent CCI consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for CCI and/or CRS.
<u>Grade 2^a</u> Fever^b with hypotension not requiring vasopressors <u>and/or</u> Hypoxia requiring low-flow oxygen^d by nasal cannula or blow by	- Immediately interrupt CCI - Upon symptom resolution, wait for 30 minutes and then restart CCI being given at the time of event onset. - If symptoms recur, discontinue CCI of this dose. - Administer symptomatic treatment.^c - For hypotension, administer IV fluid bolus as needed. - Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. - Rule out other inflammatory conditions that can mimic CRS (eg, sepsis). If there is no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH or MAS as described in Table 28. - Consider IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). - Consider anti-cytokine therapy.^e

Event	Management
	- Consider hospitalization until complete resolution of symptoms. If there is no improvement within 24 hours, manage as per Grade 3, that is, hospitalize the patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.^f - If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent CCI consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics and monitor closely for CCI and/or CRS. - If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
Grade 3^a Fever^b with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen^d by nasal cannula, face mask, non-rebreather mask, or Venturi mask	- Permanently discontinue atezolizumab and contact Medical Monitor.^f - Administer symptomatic treatment.^c - For hypotension, administer IV fluid bolus and vasopressor as needed. - Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. - Rule out other inflammatory conditions that can mimic CRS (eg, sepsis). If there is no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Table 28. - Administer IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). - Consider anti-cytokine therapy.^e - Hospitalize the patient until complete resolution of symptoms. If there is no improvement within 24 hours, manage as per Grade 4, that is, admit the patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments^g may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4^a Fever^b with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	- Permanently discontinue atezolizumab and contact Medical Monitor.^f - Administer symptomatic treatment.^c - Admit the patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. - Rule out other inflammatory conditions that can mimic CRS (eg, sepsis). If there is no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in Table 28. - Administer IV corticosteroids (eg, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).

Event	Management
	- Consider anti-cytokine therapy.^e For patients who are refractory to anti-cytokine therapy, experimental treatments^g may be considered at the discretion of the investigator and in consultation with the Medical Monitor. - Hospitalize the patient until complete resolution of symptoms.

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; CCI; IV = intravenous(ly); MAS = macrophage activation syndrome; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

^a Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI-CTCAE v5.0 should be used when reporting severity of CCI CRS, or organ toxicities associated with CRS in the eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

^b Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who develop CRS and then receive antipyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

^c Symptomatic treatment may include oral or IV antihistamines, antipyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

^d Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

^e There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors,^{51, 52} but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

^f Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor. For subsequent CCI administer oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for CCI and/or CRS. Premedication with corticosteroids and extending the CCI may also be considered after consulting the Medical Monitor and considering the benefit-risk ratio.

^g Refer to Riegler et al⁵⁴ for information on experimental treatments for CRS.

Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

Management guidelines for pancreatic events, including pancreatitis, are provided in [Table 22](#).

Table 22: Management Guidelines for Pancreatic Events Associated With Atezolizumab

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (eg, > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.^c
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset.^a • Refer patient to GI specialist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.^c

Event	Management
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.^c • Refer patient to GI specialist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Abbreviations: GI = gastrointestinal; IV = intravenous(ly).

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Management guidelines for dermatologic events are provided in [Table 23](#).

Table 23: Management Guidelines for Dermatologic Events Associated With Atezolizumab

Event	Management
Dermatologic event, Grade 1	- Continue atezolizumab. - Consider treatment with topical corticosteroids and/or other symptomatic therapy (eg, antihistamines).
Dermatologic event, Grade 2	- Continue atezolizumab. - Consider patient referral to a dermatologist for evaluation and, if indicated, biopsy. - Initiate treatment with topical corticosteroids. - Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Refer patient to dermatologist for evaluation and, if indicated, biopsy. - Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Dermatologic event, Grade 4	Permanently discontinue atezolizumab and contact Medical Monitor.^c
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens Johnson syndrome or toxic epidermal necrolysis: - Withhold atezolizumab for suspected Stevens Johnson syndrome or toxic epidermal necrolysis. - Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. - Follow the applicable treatment and management guidelines above. - If Stevens Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in [Table 24](#).

Table 24: Management Guidelines for Neurologic Disorders Associated With Atezolizumab

Event	Management
Immune-mediated neuropathy, Grade 1	- Continue atezolizumab. - Investigate etiology.
Immune-mediated neuropathy, Grade 2	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Investigate etiology. - Initiate treatment as per institutional guidelines. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Immune-mediated neuropathy, Grade 3 or 4	- Permanently discontinue atezolizumab and contact Medical Monitor.^c - Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	- Permanently discontinue atezolizumab and contact Medical Monitor.^c - Refer patient to neurologist. - Initiate treatment as per institutional guidelines. - Consider initiation of 1-2 mg/kg/day oral or IV prednisone or equivalent.

Abbreviations: IV = intravenous(ly).

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Immune-Mediated Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 25](#).

Table 25: Management Guidelines for Immune-Mediated Meningoencephalitis Associated With Atezolizumab

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor.^a • Refer patient to neurologist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Abbreviations: IV = intravenous(ly).

^a Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Renal Events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as NSAIDs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 26](#).

Table 26: Management Guidelines for Renal Events Associated With Atezolizumab

Event	Management
Renal event, Grade 1	- Continue atezolizumab. - Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to Baseline values.
Renal event, Grade 2	- Withhold atezolizumab for up to 12 weeks after event onset.^a - Refer patient to renal specialist. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event resolves to Grade 1 or better, resume atezolizumab.^b - If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c
Renal event, Grade 3 or 4	- Permanently discontinue atezolizumab and contact Medical Monitor.^c - Refer patient to renal specialist and consider renal biopsy. - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 27](#).

**Table 27: Management Guidelines for Immune-Mediated Myositis Associated With
 Atezolizumab**

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset^a and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset^a and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab.^b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^c • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.^c • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2-mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Abbreviation: IV = intravenous(ly).

^a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered potential risks for atezolizumab.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein.⁵⁵ A patient should be classified as having HLH if 5 of the following 8 criteria are met:

- Fever ≥ 38.5 °C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least 2 of the following:
 - Hemoglobin < 90 g/L (9 g/dL)
 - Platelet count $< 100 \times 10^9$ /L (100,000/ μ L)
 - Absolute neutrophil count $< 1.0 \times 10^9$ /L (1000/ μ L)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al.⁵⁶ A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least 2 of the following:
 - Platelet count $\leq 181 \times 10^9$ /L (181,000/ μ L)
 - AST ≥ 48 U/L
 - Triglycerides > 1.761 mmol/L (156 mg/dL)
 - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in [Table 28](#).

Table 28: Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome Associated With Atezolizumab

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Abbreviations: HLH = hemophagocytic lymphohistiocytosis; IV = intravenous(ly); MAS = macrophage activation syndrome.

7.5.1.2. Management of Adverse Events Associated With Atezolizumab Plus Bevacizumab

Table 29 provides guidelines for the management of patients who experience AEs associated with atezolizumab plus bevacizumab.

Table 29: Management Guidelines for Adverse Events Associated With Atezolizumab Plus Bevacizumab

Event	Management
CCI CRS, anaphylaxis, and hypersensitivity reaction	
General guidance	• Guidelines for management of CCI and CRS for atezolizumab are provided in Table 21. • For anaphylaxis precautions, see Appendix 6. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and bevacizumab.
CCI to bevacizumab, Grade 1	• Continue bevacizumab. • Systemic intervention is not indicated.
CCI to bevacizumab, Grade 2	• Reduce CCI to $\leq 50\%$ or interrupt CCI at the discretion of the Investigator per medical judgment. • If the CCI is interrupted, it may be resumed at $\leq 50\%$ of the CCI prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the CCI if well tolerated. CCI may be restarted at the CCI during the next cycle.

Event	Management
CCI to bevacizumab, Grade 3 or 4	• Stop CCI and permanently discontinue bevacizumab. • Administer aggressive symptomatic treatment (eg, oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen) if clinically indicated.
Hemophagocytic lymphohistiocytosis or macrophage activation syndrome	• Follow guidelines for atezolizumab in Table 28. • Withhold all treatment and contact Medical Monitor for guidance.
Gastrointestinal toxicity	
Gastrointestinal perforation, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • Initiate treatment per institutional guidelines. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab.^a
Bowel obstruction, Grade 2	• Atezolizumab may be continued at the discretion of the Investigator. • Withhold bevacizumab for partial obstruction requiring medical intervention. • Bevacizumab may be restarted upon complete resolution of event.
Bowel obstruction, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the Investigator. • Withhold bevacizumab for complete obstruction. • If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at the Investigator's discretion.
Hypertension	
General guidance	• Treat with antihypertensive medication, as needed.
Hypertension, Grade 1	• Continue atezolizumab and bevacizumab. • Consider increased blood pressure monitoring
Hypertension, Grade 2	• Continue atezolizumab. • If asymptomatic, begin or modify Baseline antihypertensive therapy and continue bevacizumab. • If symptomatic, start or adjust antihypertensive therapy. Hold bevacizumab until asymptomatic.
Hypertension, Grade 3	• Continue atezolizumab. • Modify existing antihypertensive therapy (> 1 drug or more intensive therapy than previously indicated). • Withhold bevacizumab until symptoms resolve AND blood pressure < 160/90 mmHg.

Event	Management
Hypertension, Grade 4	• Atezolizumab may be continued at the discretion of the Investigator. • Permanently discontinue bevacizumab.
Hemorrhage	
Hemorrhage, Grade 3 or 4 (excluding cerebral hemorrhage)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
Cerebral hemorrhage, any grade	• Atezolizumab may be continued at the discretion of the Investigator. • Permanently discontinue bevacizumab.
Grade ≥ 2 hemoptysis (≥ 2.5 mL of bright red blood per episode)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
Bleeding in patients on full-dose anticoagulant therapy (allowed only for certain patients who develop venous thromboembolism on trial)	• Continue atezolizumab. • Permanently discontinue bevacizumab.
Thromboembolic events	
Venous thromboembolic event Grade 3	• Atezolizumab may be continued at the discretion of the Investigator. • Withhold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. The use of direct oral anticoagulants is not recommended. • If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full-dose anticoagulation IF all of the criteria below are met: - The patient must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions). - The patient must not have had hemorrhagic events Grade > 2 while in the trial. - The patient must be on stable dose of unfractionated heparin or low molecular weight heparin prior to restarting bevacizumab. • If thromboemboli worsen/recur upon resumption of study drug, discontinue bevacizumab.
Venous thromboembolic event, Grade 4	• Atezolizumab may be continued at the discretion of the Investigator. • Permanently discontinue bevacizumab.

Event	Management
Arterial thromboembolic event, any grade	• Atezolizumab may be continued at the discretion of the investigator. • Permanently discontinue bevacizumab.
Proteinuria^b	
Proteinuria, Grade 1 (1+ by UA or dipstick; urinary protein < 1.0 g/24 hours)	• Continue atezolizumab and bevacizumab.
Proteinuria, Grade 2 (2+ and 3+ by UA or dipstick; urinary protein 1.0-3.4 g/24 hours)	• Continue atezolizumab. • For 2+ dipstick: Continue bevacizumab and collect 24-hour urine protein prior to subsequent bevacizumab administration. • For 3+ dipstick: Obtain 24-hour urine prior to administering bevacizumab. • Withhold bevacizumab for urinary protein ≥ 2 g/24 hours. • If bevacizumab is withheld and urine protein improves to < 2 g/24 hours within 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Proteinuria, Grade 3 (4+ by dipstick; urinary protein ≥ 3.5 g/24 hours) with no diagnosis of nephrotic syndrome	• Atezolizumab may be continued at the discretion of the Investigator. • Withhold bevacizumab. • If urine protein improves to < 2 g/24 hours within 42 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab.
Nephrotic syndrome, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the Investigator. • Permanently discontinue bevacizumab.
Fistula	
Tracheoesophageal fistula, any grade	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab.^a
Fistula (non- tracheoesophageal), Grade 4	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab.^a
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Atezolizumab may be continued at the discretion of the Investigator. • Permanently discontinue bevacizumab.

Event	Management
Congestive heart failure	
Congestive heart failure, Grade 3 or 4	• Atezolizumab may be continued at the discretion of the Investigator. • Permanently discontinue bevacizumab.
Posterior reversible encephalopathy syndrome (PRES)/Reversible posterior leukoencephalopathy syndrome (RPLS)	
PRES/RPLS, any grade confirmed by MRI	• Withhold atezolizumab. • Permanently discontinue bevacizumab. • If event improves, consider resuming atezolizumab. If not, permanently discontinue atezolizumab.^a
Hepatic events	
AST/ALT is within normal limits at Baseline and increases to $> 3 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$ <u>or</u> AST/ALT is $> \text{ULN}$ to $\leq 3 \times \text{ULN}$ at Baseline and increases to $> 5 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$ <u>or</u> AST/ALT is $> 3 \times \text{ULN}$ to $5 \times \text{ULN}$ at Baseline and increases to $> 8 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$	• Monitor LFTs more frequently until return to Baseline values or Grade 1 or better. • Withhold atezolizumab for up to 12 weeks after event onset.^c • Continue bevacizumab. • For events of > 5 days' duration, consider initiating treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Baseline or to Grade 1 or better, resume atezolizumab.^d • If event does not resolve to Baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.^a
AST or ALT increases to $> 10 \times \text{ULN}$ or total bilirubin increases to $> 3 \times \text{ULN}$	• Permanently discontinue atezolizumab and contact Medical Monitor.^a • Withhold bevacizumab. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over ≥ 1 month. • If event resolves to Grade 1 within 42 days, resume bevacizumab at the discretion of Investigator. If not, permanently discontinue bevacizumab and contact Medical Monitor.^a

Event	Management
Endocrine disorders	
Asymptomatic hypothyroidism	- Follow guidelines for atezolizumab in Table 18. - Continue bevacizumab.
Symptomatic hypothyroidism	- Follow guidelines for atezolizumab in Table 18. - Continue bevacizumab.
Asymptomatic hyperthyroidism	TSH $\geq$ 0.1 mU/L and $<$ 0.5 mU/L: - Follow guidelines for atezolizumab in Table 18. - Continue bevacizumab. TSH $<$ 0.1 mU/L: - Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	- Follow guidelines for atezolizumab in Table 18. - Bevacizumab may continue at the discretion of the Investigator per medical judgment.
Neurologic disorder	
Immune-mediated meningoencephalitis, any grade	- Follow guidelines for atezolizumab in Table 25. - Withhold bevacizumab. - If patient stabilizes within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^a
Dermatologic events	
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	- Follow guidelines for atezolizumab in Table 23. - Withhold bevacizumab. - If event resolves to Grade 1 or better, resume bevacizumab. - Permanently discontinue bevacizumab if withheld for $>$ 42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	- Follow guidelines for atezolizumab in Section 7.5.1.1. - Continue bevacizumab.
Grade 3 or 4	- Follow guidelines for atezolizumab in Section 7.5.1.1. - Withhold bevacizumab. - If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^a

Event	Management
Bevacizumab-related toxicities not described above	
Grade 1 or 2	Continue atezolizumab and bevacizumab.
Grade 3	- Continue atezolizumab. - Withhold bevacizumab. - If event resolves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^a
Grade 4	- Withhold atezolizumab and bevacizumab. - If event improves and Medical Monitor agrees that atezolizumab should be continued, resume atezolizumab. If not, permanently discontinue atezolizumab. - If event improves to Grade 2 or better within 42 days, resume bevacizumab. If not, permanently discontinue bevacizumab.^a

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; GI = gastrointestinal; CCI = central nervous system; IV = intravenous(ly); LFT = liver function test; MRI = magnetic resonance imaging; TSH = thyroid stimulating hormone; UA = urinalysis; ULN = upper limit of normal.

^a Resumption of treatment may be considered if the Investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement.

^b Institutional protocols acceptable.

^c Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

^d If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

7.6. Drug Accountability

The Investigator or designee is responsible for taking an inventory of each shipment of investigational product(s) received and comparing it with the accompanying drug order form.

All unused study drug(s) will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of any study drug at the clinical trial site per site procedures, or if necessary, all study drug will be returned to the Sponsor, or its designee. Disposition of all study drug should be documented, including any study drug that is lost or damaged.

7.7. Assignment to Treatment

Patients in the Lead-In will receive CHS-388, atezolizumab, and bevacizumab.

Patients in the Randomized Phase will be randomized into Arm A or Arm B with a 1:1 allocation and stratified by geographic region (Asia excluding Japan vs. rest of world) and BCLC stage (B or C).

Patients randomized to Arm A will receive CHS-388, atezolizumab, and bevacizumab.

Patients randomized to Arm B will receive placebo, atezolizumab, and bevacizumab.

All study drugs will be administered q3 weeks on Day 1 of each 21-day cycle.

8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

8.1. Adverse Events

8.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug, or with trial participation, whether or not considered related to study drug.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

Adverse events include worsening of a preexisting medical condition as well as clinically significant changes from Baseline laboratory values/conditions. Worsening of the preexisting medical condition (eg, diabetes, hypertension) means that it has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A preexisting condition that has not worsened during the trial is not considered an AE.

8.1.2. Definition of a Serious Adverse Event

An AE or suspected adverse reaction is termed “serious” if according to the Investigator or Sponsor, it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
 - Elective or preplanned treatment for a preexisting condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF) is not considered an SAE
 - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly/birth defect
- Is considered an important medical event
 - If an AE does not meet one of the serious criteria, but the Investigator or Sponsor considers an event to be clinically important, the event could be classified as an SAE under the criterion of “important medical event.” Examples of such medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Per NCI-CTCAE version 5.0, if death is due to an AE (eg, Cardiac disorders: cardiac arrest; infection, pulmonary embolism), it should be reported as a Grade 5 event under that system organ class and preferred term. However, if death is due to disease progression but cannot be attributed to a specific NCI-CTCAE term associated with Grade 5, the AE should be reported as NCI-CTCAE Preferred Term “disease progression” found in the system organ class, “General disorders and administration site conditions.” Evidence that the death was a manifestation of the underlying disease (eg, radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

8.1.3. Definition of Adverse Events of Special Interest

There are no adverse events of special interest (AESIs) for CHS-388 in this trial. The following are considered AESIs for the combination of atezolizumab and bevacizumab:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Suspected transmission of an infectious agent by the study drug, defined as follows:
 - Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study drug is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, CCI, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (eg, uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (eg, atrial fibrillation, myocarditis, pericarditis)
- Vasculitis

- Autoimmune hemolytic anemia
- Severe cutaneous reactions (eg, Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscess, or fistula
- Grade ≥ 2 non-GI fistula or abscess
- Grade ≥ 3 wound-healing complication
- Hemorrhage: any grade central nervous system bleeding, Grade ≥ 2 hemoptysis, other Grade ≥ 3 hemorrhagic event
- Any arterial thromboembolic event
- Grade ≥ 3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome
- Grade ≥ 3 congestive heart failure

8.2. Procedures for Recording and Reporting Adverse Events

8.2.1. Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each trial visit. All SAEs occurring in patients will be recorded in the eCRF from the time of signing the ICF through the Safety Follow-up Visit or 90 days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later. All AEs occurring in treated patients will be recorded in the eCRF from the time of completion of the initial Screening assessments through 30 days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later. An AE will be followed until it is either resolved, has returned to Baseline, or is determined to be a stable or chronic condition. All SAEs occurring from the signing of ICF through 90 days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later, will be processed as outlined in [Section 8.2.2](#).

At each required visit during the trial, all AEs that have occurred since the previous visit must be reviewed by the Investigator. The Investigator must determine if the AE is serious or nonserious.

The Investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s) if known
 - If not known at time of the report, record the signs and/or symptoms as AEs and provide an updated report with diagnosis when obtained.
- Dates of onset and resolution
- Severity as defined per protocol
- Assessment of relatedness to each study drug

- Action taken with each study drug as a result of the AE

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause (eg, for dehydration due to diarrhea, the AE would be diarrhea). However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events (eg, sepsis secondary to pneumonia, both events should be recorded).

The signs and symptoms of PD that meet the AE criteria should be reported as specific AEs, and not as disease progression.

8.2.1.1. Relationship to Study Drug

The Investigator must assess whether the AE may be related to each study drug or study mandated procedure, when applicable. The relationship is defined below:

Relationship assessments that indicate the event is “Not Drug Related”:

- None: The event is related to an etiology other than the study drug administration (the alternative etiology must be documented in the trial patient’s medical record).
- Remote: The event is unlikely to be related to the study drug and likely to be related to factors other than study product.

Relationship assessments that indicate the event is “Drug Related”:

- Possible: There is an association between the event and the administration of study drug, and there is a plausible mechanism for the event to be related to the study drug; but there may also be alternative etiology, such as characteristics of the patient’s clinical status or underlying disease.
- Probable: There is an association between the event and the administration of study drug, there is a plausible mechanism for the event to be related to the study drug, and the event could not be reasonably explained by known characteristics of the patient’s clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of study drug, there is a plausible mechanism for the event to be related to the study drug, and causes other than study drug have been ruled out and/or the event reappeared on re-exposure to study drug.

8.2.1.2. Adverse Event Severity

The Investigator will assess the Grade of the AE per the NCI-CTCAE version 5.0 or higher. Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to AE

Note: It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 8.1.2 above.

8.2.1.3. Abnormal Laboratory and Electrocardiogram Values

The Investigator is responsible for reviewing clinical laboratory test and ECG results and determining whether an abnormal value in a patient represents a clinically significant change from patient's Baseline value. In general, abnormal laboratory findings and ECGs without clinical significance (based on the Investigator's judgment) should not be recorded as AEs. In general, an abnormal laboratory test and ECG results should be reported as an AE if the laboratory result:

- Requires an adjustment or discontinuation of study drug
- Requires treatment or adjustment to concomitant medications
- Is considered to be an AE by the Investigator

Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ Baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). The patient population for this trial consists of patients with decreased hepatic function who may exhibit abnormal liver function test results, some of which may meet Hy's Law criteria prior to enrollment in the trial. The following modified Hy's Law criteria are for the purpose of determining what may constitute a drug-induced liver injury for this trial population and defining those cases that require expedited reporting to the health authorities in relation to Hy's Law.

Investigators must report the occurrence of either of the following as an AE:

- Treatment-emergent ALT or AST $> 3 \times$ Baseline value in combination with either an elevated total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $> 3 \times$ Baseline value in combination with clinical jaundice

The most appropriate diagnosis or, if a diagnosis cannot be established, the abnormal laboratory values should be recorded in the eCRF and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as an SAE or an AESI (see Section 8.2.2).

8.2.1.4. Medication Errors, Misuse, and Abuse of Study Drug

Overdose, medication error, misuse, and abuse are defined as follows:

- Medication error: refers to an unintentional error in dispensing or administration of study drug not in accordance with the protocol

- Off-label use: relates to situations where the study drug is intentionally used for medical purpose not in accordance with the protocol
- Misuse: refers to situations where the study drug is intentionally and inappropriately used not in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional excessive use of the study drug, which is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to the exposure to the study drug because of one's professional or non-professional occupation

Overdoses, medication errors, abuse, or misuse will be collected as part of investigational medicinal product dosing information and/or as a protocol violation, as required.

8.2.2. Reporting of Serious Adverse Events and Adverse Events of Special Interest

An SAE/AESI Report Form will be completed in electronic data capture (EDC) and submitted to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to study drug, from the time of signing ICF through 90 days after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later.

In the event EDC is unavailable, the paper SAE/AESI Report Form and/or the Pregnancy Report Form, as applicable, must be filled out by the Investigator and sent via telephone or email within 24 hours of awareness of the event to the dedicated Coherus Drug Safety telephone number or email.

Contacts for SAE reporting are as follows:

Coherus Drug Safety

- Email: coheruspv@parexel.com
- Fax: 1-781-434-5957
- Telephone: 1-781-434-5010

As soon as EDC is available, the Investigator or site personnel should enter the event from the paper SAE report form, including any updated information into EDC. The site will ensure that the date of awareness of the SAE (Day 0) in EDC reflects the awareness date from the paper SAE form.

Please refer to the SAE Report Form and completion guidelines for more detailed instructions.

The initial SAE report form must be as complete as possible, including details of the current illness and SAE, and an assessment of the relationship between the event and study drug. Additional information relating to a previously reported SAE must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor, to provide clarifications or additional information.

If the Investigator becomes aware of an SAE considered related to study drug by the Investigator occurring more than 90 days after the last dose of CHS-388/placebo, the SAE must be reported as described above.

8.2.2.1. Reporting of Serious Adverse Events to Regulatory Authorities, Ethics Committee, and Institutional Review Board

The Sponsor or designee will determine expectedness for each reported SAE based on the appropriate reference safety information for the study drugs per local requirements. The Sponsor or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs, per local requirements.

The Sponsor or designee shall notify the Investigator of serious, related, and unexpected AE(s) submitted to the regulatory agencies, per local country requirements.

The Investigator shall notify the Central Ethics Committees of serious, related, and unexpected AE(s), or significant risks to patients, per country requirements.

The Investigator will notify the appropriate institutional review board (IRB)/local ethics committees of serious, related, and unexpected AE(s), or significant risks to patients, per local country requirements. The Investigator must keep copies of all AE information on file, including correspondence with the Sponsor or IRBs/ethics committees.

8.2.2.2. Reporting Adverse Events of Special Interest

AESIs for this trial are defined in Section 8.1.3. The Investigator should report both serious and nonserious AESIs to the Sponsor using the same methods as described for reporting SAEs.

8.2.3. Pregnancy and In Utero Drug Exposure

CHS-388 has not been evaluated in pregnant or nursing women. Thus, pregnant women or WCBP who do not agree to use effective contraception are excluded from this trial (see Section 6.7.5 and Section 6.1.9 for instructions on birth control and pregnancy testing, respectively).

Pregnancies occurring in female patients or female partners of male patients are considered immediately reportable events if the pregnancy occurs during the study treatment period through 6 months after the last dose of CHS-388/placebo, atezolizumab, or bevacizumab, whichever is later. If a pregnancy occurs in a patient, study drug must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy using the Pregnancy Notification Form.

The Investigator will follow the pregnant patient until completion of the pregnancy and must notify the Sponsor of the pregnancy outcome within 24 hours of the Investigator's knowledge of the outcome. The Investigator will provide this information on the Pregnancy Outcome Report Form. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant patient experiences an SAE during pregnancy, or the outcome of the pregnancy meets any of the serious criteria (ie, spontaneous abortion [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 reporting SAEs (ie, report the event to the Sponsor or designee within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to the Sponsor or designee. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported to the Sponsor or designee. Please refer to the Pregnancy Notification Form or Pregnancy Outcome Form and associated completion guidelines on where and how to submit the forms

9. STATISTICAL METHODS

Details of the statistical methods for this trial will be documented in a Statistical Analysis Plan (SAP). The SAP may modify the statistical methods outlined in the protocol; however, any major modification will also be reflected in a protocol amendment. The Lead-In and the Randomized Phase will be analyzed in separate study outputs.

9.1. Sample Size

Trial SRF388-201 will enroll a total of approximately 134 patients; approximately 30 patients in the Lead-In followed by the Randomized Phase enrolling approximately 104 patients in a 1:1 randomization stratified by geographic location (Asia excluding Japan vs. rest of world) and BCLC stage (B or C) to assess a primary endpoint of PFS.

In the sample size calculation, the HR was calculated using the Weibull distribution with increasing hazard ($\kappa=1.92$), based on the shape of PFS curves in the literature. Of note, the exponential distribution is a special case of the Weibull distribution in that it has a constant hazard. Utilizing a larger alpha (1-sided alpha at 0.05, instead of a 1-sided alpha at 0.025) and appropriately modeling the HR based on the shape of the PFS curve for these patients, the protocol utilizes increased PFS as the primary endpoint. A clinically meaningful difference in median survival of 2.1 months (6.9 months vs 9 months) and the calculation of HR from a Weibull distribution of $[mPFS(\text{Control})/mPFS(\text{Experimental})]^{\kappa} = (6.9/9)^{1.92}$ result in the estimated HR of 0.6. Once approximately half of the planned PFS events (ie, 49 of 97) have occurred, an interim analysis for futility only will be performed. If the $HR \geq 1$, then the trial will stop for futility.

9.2. Objectives and Endpoints

The trial objectives and endpoints are summarized in [Table 30](#). All objectives and endpoints are for both the Lead-In and Randomized Phase unless otherwise specified.

Table 30: Objectives and Endpoints in Trial SRF388-201

Primary Objectives	Primary Endpoints
Lead-In: - To evaluate the safety and tolerability of CHS-388 in combination with atezolizumab + bevacizumab Randomized Phase: - To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab as measured by PFS	Lead-In: - Nature, frequency, and severity of AEs per NCI-CTCAE version 5.0 or higher - Timing of AEs Randomized Phase: - PFS, defined as time from randomization to occurrence of PD or death from any cause (whichever occurs first), as determined by Investigator review according to RECIST v1.1

Secondary Objectives	Secondary Endpoints
Efficacy Objectives	Efficacy Endpoints
• To evaluate preliminary measures of efficacy of CHS-388 in combination with atezolizumab + bevacizumab in the Lead-In • To evaluate additional measures of efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab in the Randomized Phase • To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab according to serum EBI3 levels in the Lead-In • To evaluate the efficacy of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab according to serum EBI3 levels in the Randomized Phase	• PFS, defined as time from study drug initiation to occurrence of PD or death from any cause (whichever occurs first), as determined by Investigator review according to RECIST v1.1 (Lead-In only) • PFS, defined as time from study drug initiation (Lead-In) or randomization to occurrence of PD or death from any cause (whichever occurs first), as determined by Investigator review according to HCC mRECIST • ORR as determined by Investigator review according to: – RECIST v1.1 – HCC mRECIST • DoR, defined as time from initial documented objective response to PD or death from any cause (whichever occurs first), as determined by Investigator review according to: – RECIST v1.1 – HCC mRECIST • DCR, defined as the proportion of patients who experience best overall response of CR, PR, or SD • TTP, defined as time from study drug initiation (Lead-In) or randomization to occurrence of disease progression, as determined by Investigator review according to: – RECIST v1.1 – HCC mRECIST • OS, defined as time from study drug initiation (Lead-In) or randomization to death from any cause • Time to response, defined as time from study drug initiation (Lead-In) or randomization to initial documented objective response, as determined by Investigator review according to: – RECIST v1.1 – HCC mRECIST

	- Time on therapy, defined as time from study drug initiation (Lead-In) or randomization to last treatment - PFS, ORR, TTP, and OS by serum EBI3 concentrations
Safety Objective	Safety Endpoints
To evaluate the safety and tolerability of CHS-388 in combination with atezolizumab + bevacizumab compared to placebo in combination with atezolizumab + bevacizumab in the Randomized Phase	- Nature, frequency, and severity of AEs per NCI-CTCAE version 5.0 or higher - Timing of AEs
Immunogenicity Objectives	Immunogenicity Endpoints
- To characterize the immunogenicity of CHS-388 and atezolizumab - To explore potential correlations between immunogenicity and efficacy, safety, and PK outcomes	- Incidence of CHS-388 ADAs - Incidence of atezolizumab ADAs - Efficacy, safety, and PK endpoints by ADA status
Pharmacokinetic Objectives	Pharmacokinetic Endpoints
- To characterize the PK profile of CHS-388 when given in combination with atezolizumab + bevacizumab - To explore the potential PK impact from drug interaction	- Serum concentrations of CHS-388 - Serum concentrations of atezolizumab
Exploratory Biomarker Objectives	Exploratory Biomarker Endpoints
- To identify and evaluate potential blood or tissue biomarkers of response, resistance, and/or safety - To evaluate the effects of CHS-388 in combination with atezolizumab + bevacizumab on peripheral blood immune cell subsets and circulating cytokines and chemokines	- Assessment of selected blood-based and tumor tissue biomarkers, which may include cytokines, immune cell population subset enumeration and evaluation, PD-L1 expression, gene and protein expression levels, DNA mutation and copy number variations, and correlation of Baseline levels and changes in these markers with clinical outcomes (eg, PFS, ORR) - Changes in peripheral blood immune cell populations by flow cytometry and gene expression

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CR = complete response; DCR = disease control rate; DoR = duration of response; EBI3 = Epstein-Barr virus induced gene; HCC = hepatocellular carcinoma; mRECIST = modified Response Evaluation Criteria in Solid Tumors; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; PD = progressive disease; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; SD = stable disease; TTP = time to progression.

9.3. Analysis Sets

The main population analysis sets are defined in this section. Additional analysis sets may be defined in the SAP.

9.3.1. Intent-to-Treat Analysis Set

The Intent-to-Treat Analysis Set is defined as all patients as randomized. This analysis set will be the primary analysis set for the efficacy analyses for the Randomized Phase. Those without any post-treatment assessment are included and considered as non-responders in this analysis.

9.3.2. Safety Analysis Sets

The Safety Lead-In Evaluable Analysis Set is defined as patients enrolled in the open-label Safety Lead-In, who either experienced a Grade ≥ 3 related AE during the first cycle of therapy (Day 1-21) or who completed at least 50% of the prescribed combination therapy doses. The aggregate safety data of these patients during Cycle 1 will be reviewed by the SRC prior to initiating enrollment in the Lead-In Expansion.

The Lead-In Safety Analysis Set is defined as the patients enrolled in the open-label Lead-In (Safety Lead-In plus the Lead-In Expansion) who received any amount of study drug (CHS-388, atezolizumab, or bevacizumab). This analysis set will be the primary analysis set for all safety endpoints in the Lead-In.

The Randomized Safety Analysis Set is defined as all patients who received any amount of study drug (CHS-388/placebo, atezolizumab, or bevacizumab) in the Randomized Phase, with treatment group designated per actual study drug received. This analysis set will be the primary analysis set for all safety endpoints in the Randomized Phase.

9.3.3. Response-Evaluable Analysis Set

The Response-Evaluable Analysis Set is defined for the Lead-In as all Lead-In patients with measurable disease at baseline who received ≥ 1 dose of all assigned study drugs and had ≥ 1 post-Baseline response assessment or who discontinued the treatment phase due to radiographic or symptomatic disease progression (including death caused by disease progression) within 9 weeks after the first dose of study drug. This analysis set will be the primary analysis set for the efficacy endpoints for the Lead-In.

For the Randomized Phase, the Response-Evaluable Analysis Set is a subset of the Intent-to-Treat Analysis Set defined as all patients with measurable disease at Baseline who received ≥ 1 dose of all assigned study drugs and had ≥ 1 post-Baseline response assessment or who discontinued the treatment phase due to radiographic or symptomatic disease progression (including death caused by disease progression) within 9 weeks after the first dose of study drug. This analysis set will be used as a sensitivity analysis for efficacy endpoints for the Randomized Phase.

9.3.4. Pharmacokinetics Analysis Sets

The PK Analysis Sets for CHS-388 and atezolizumab are defined as all patients who received ≥ 1 dose of CHS-388 or atezolizumab, respectively, and had ≥ 1 measurable concentration. These analysis sets will be used for the PK endpoints.

9.3.5. EBI3 Biomarker Analysis Set

The EBI3 Biomarker Analysis Set is defined as all enrolled patients who received ≥ 1 dose of CHS-388 and had ≥ 1 adequate EBI3 assessment, including a Screening or C1D1 assessment.

9.4. Background Characteristics

9.4.1. Patient Disposition

The number and percentage of patients in each disposition category (eg, enrolled, included in each Analysis Set, completing a given number of treatment cycles, discontinuing treatment, and discontinuing the trial, with a breakdown of the reasons for discontinuation) will be summarized overall and by treatment group.

9.4.2. Demographic and Baseline Characteristics

The following demographics and Baseline characteristics will be summarized overall and by treatment group for the Safety Analysis Set: age, sex, race, geographic region, ECOG performance status, Child-Pugh score, BCLC stage, viral status, alcohol use, extent of local and metastatic disease, extent of portal vein invasion, presence of bile duct invasion, AFP level, and PD-L1 expression.

9.5. Study Drug Exposure and Compliance

Total number of cycles is defined as the maximum number of treatment cycles that a patient receives. Total cumulative dose (mg) is the sum of the actual doses that the patient receives across cycles. Total planned dose (mg) is the sum of the planned doses. The total number of cycles, total cumulative dose (mg), and total planned dose (mg) will be summarized.

The study drug exposure will be summarized for each study drug by treatment group based on the Safety Analysis Set.

9.6. Efficacy Analyses

The Randomized Phase primary endpoint of PFS will be assessed according to RECIST v1.1, as determined by Investigator review.

Multivariate analyses will adjust for potentially confounding factors that are relevant for prognosis such as severity of liver damage (BCLC stage), macrovascular invasion, extrahepatic metastases, ECOG performance status, AFP levels, and viral status.

Forest plots will be used to present PFS and OS by Baseline demographics and disease characteristics including but not limited to age (median), sex (female, male, undifferentiated), race, geographic region, ECOG performance status, Child-Pugh score (A5, A6), BCLC stage (B, C), HCC etiology (eg, viral, alcohol, other), viral status (HBV, HCV, uninfected/non-viral), alcohol use (current, never, previous), extent of disease (macrovascular invasion, extrahepatic invasion, both, neither; invasion of bile duct, invasion of main portal vein), degree of liver occupation ($< 50\%$, $\geq 50\%$), AFP (< 400 ng/mL or ≥ 400 ng/mL), and PD-L1 expression ($\geq 1\%$, $< 1\%$, missing).

Landmark analyses at 6 months, 12 months, 18 months, and 24 months will be conducted.

Additional planned analyses include PFS according to HCC mRECIST as determined by Investigator review; ORR, DoR, DCR (defined as the proportion of patients who experience a best overall response of CR, PR, or SD), TTP, and time to response according to RECIST v1.1 and HCC mRECIST and as determined by Investigator review; time on therapy; and PFS, ORR, TTP, and OS by serum EBI3 concentrations, which will be analyzed as secondary endpoints.

The number and percentage of patients with best overall response per RECIST v1.1 and HCC mRECIST in each of the response categories will be presented for each treatment group. ORR will be estimated by the percentage of patients achieving a best overall response of CR or PR. The estimated ORR, along with the 2-sided 90% and 95% exact confidence intervals will be provided.

For efficacy endpoints derived from progression and/or response status, disease assessments after the start of new anticancer therapy will be excluded from consideration.

All time-to-event endpoints will be summarized and estimated via the Kaplan-Meier method if the number of events is adequate.

9.7. Safety Endpoints

The Safety Analysis Set will be used to evaluate all safety endpoints unless the endpoints are applicable to only selected patients.

9.7.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher and will be graded according to NCI-CTCAE version 5.0 or higher.

The numbers and types of AEs and SAEs experienced will be summarized in by-patient listings. The listings will include the description, severity, and relationship of the events to study drug (CHS-388/placebo, atezolizumab, and/or bevacizumab).

Summaries of AEs will be based on TEAEs. A TEAE is an AE that emerges or worsens in the period from the first dose of study drug to 30 days after the last dose of study drug.

TEAEs will be summarized by treatment arm, overall, by frequency, and by MedDRA system organ class and preferred term. Separate tabulations will also be produced for TEAEs assessed as related to study drug, TEAEs that led to treatment discontinuation, TEAEs that led to death, AEs of special interest, and TEAEs Grade ≥ 3 in severity. Treatment-emergent SAEs and SAEs related to study drug will also be tabulated.

Shifts in grade (per NCI-CTCAE version 5.0 or higher) from Baseline to the maximum post-Baseline grade will be summarized.

9.7.2. Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using International System units.

Shifts in grade (per NCI-CTCAE version 5.0 or higher) from Baseline to the maximum post-Baseline grade will be summarized by treatment group for applicable laboratory data. Laboratory values $\geq$ Grade 3 in severity will be tabulated by treatment group.

A listing of individual patient hematology, serum chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

In addition, to evaluate if there is any potential risk of drug-induced liver injury in HCC patients, a listing for all cases meeting the potential Hy's Law criteria, defined as a total bilirubin increase by $> 2 \times \text{ULN}$ within 7 days after ALT or AST increased by $3 \times \text{Baseline value}$, will be provided.

9.8. Pharmacokinetic Analyses

Serum samples will be analyzed for CHS-388 concentrations using a validated ligand-binding-based method. PK parameters based on the actual sample collection times will be determined using standard noncompartmental methods using the PK Analysis Set. The PK parameters to be assessed include but are not necessarily limited to the following:

$C_{\max}$	Maximum observed serum concentration
$t_{\max}$	Time of maximum observed serum concentration
$AUC_{0-\text{last}}$	Area under the serum concentration-time curve from time zero to the last quantifiable time point
$t_{1/2}$	Terminal elimination half-life

Evaluations of PK data will include maintenance concentration, accumulation upon multiple-dose administration, and immunogenicity analysis, when appropriate. Blood samples will be collected for atezolizumab concentration analysis. Due to the limitations of sparse sampling, PK evaluation of atezolizumab will be limited to the maintenance concentrations and descriptive statistics. Additional details on the PK analyses will be provided in the SAP.

9.9. Biomarker Analyses

Biomarker analyses will generally be descriptive in nature. Summary tabulations may be produced using the EBI3 Biomarker Analysis Set if data from a sufficient number of patients are collected. Additional details on the biomarker analyses will be provided in the SAP. A receiver operating characteristic curve may be used to identify an appropriate and potentially predictive cutoff for subpopulation selection.

Additional biomarkers measured in serum, plasma, blood, and tumor tissues will be analyzed in an exploratory fashion. These exploratory analyses may or may not be presented formally. If presented, they will be limited to biomarkers for which data from a sufficient number of patients are available.

10. TRIAL ADMINISTRATION

10.1. Good Clinical Practice Statement

This trial is to be performed in accordance with the protocol, the Declaration of Helsinki, the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and all applicable local regulatory requirements.

10.2. Informed Consent

The Sponsor or its designee will provide a sample patient ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH and GCP and must adhere to the IRB/independent ethics committee (IEC) requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or his/her staff will explain the nature of the trial, its purpose and associated procedures, the expected duration, and the potential risks involved to the patient before enrollment. The Investigator or designee will obtain written, informed consent. The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the trial at any time without any disadvantage and without having to provide a reason for this decision. After the discussion regarding the trial, a patient will be asked if they are willing to sign and personally date a statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the trial. A copy of the signed and dated ICF will be provided to the patient. The signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol which necessitates a change to the content of the patient's informed consent. The Investigator will inform the patients of changes in a timely manner and will ask the patients to confirm continuation of their participation in the trial by their signature on the revised ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial ICF should be forwarded to the Sponsor.

10.3. Patient Confidentiality

The written ICF will explain that trial data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the Sponsor or its representative(s) will be identified by patient number and trial code.

The written ICF will also explain that for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, and an IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the trial that include the patient's medical history.

The Investigator must ensure that the patients' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by their assigned patient number and trial code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

10.4. Institutional Review Board/Ethics Committee Requirements

The final trial protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC at each clinical trial site. The Principal Investigator must submit written approval to the Sponsor before he or she can enroll any patient into the trial.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit patients for the trial. The protocol must be reapproved by the IRB/IEC annually or as applicable.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

10.5. Case Report Forms and Source Documentation

Electronic CRFs will be provided for the recording of all data. The Principal Investigator/subinvestigator or designee will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided by the Sponsor.

10.6. Sponsor Monitoring

Before the first patient is enrolled into the trial, a representative of the Sponsor will visit the trial site in person, or remotely as COVID restrictions persist, to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the trial) their responsibilities about the protocol and the responsibilities of the Sponsor

During the conduct of the trial, a representative of the Sponsor will have regular contact with the clinical trial site and have regular visits to the clinical trial site in person, or remotely as COVID restrictions persist, to:

- Provide information and support the Principal Investigator
- Confirm that the facilities remain acceptable
- Confirm that the trial team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each patient

10.7. Data Monitoring Committee

The IDMC will review the unblinded safety data for the first 20 patients enrolled (~10 patients per arm in the Randomized Phase) after they have completed 1 cycle of treatment. Trial enrollment will continue without pause during IDMC data review of these first 20 patients in the Randomized Phase as well as during subsequent periodic IDMC safety reviews. The IDMC will periodically review all available unblinded safety information and recommend whether the trial should continue, should continue with modifications, or should be stopped based on their review of the data. The IDMC will review the interim analysis for futility once approximately 50% of the expected PFS events occur.

10.8. Quality Assurance

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IRB/IECs may conduct quality assurance audits at any time during or after a trial. The Investigator must agree to allow auditors direct access to all trial-related documents including source documents and must agree to allocate his or her time and the time of his or her trial staff to the auditors to discuss findings and issues.

10.9. Trial or Clinical Site Termination

The Sponsor, or designee, reserves the right to terminate the trial or a clinical trial site at any time. Conditions that may warrant termination of the trial include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the trial
- The decision on the part of the Sponsor to suspend or discontinue testing the study drug
- Failure of the Investigator to comply with GCP
- Submission of knowingly false information from the clinical trial site to the Sponsor or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the trial, the Sponsor and the Investigator(s) will ensure that adequate consideration is given to the protection of the patients' interests.

10.10. Duration of the Trial, Expected Duration of Patient Participation, and End of Trial

Patients will continue study treatment for up to 2 years or until documented disease progression or unacceptable toxicity. Patients may remain on study drug longer than 2 years with agreement from the trial Investigator and Sponsor.

10.11. Records Retention

All correspondence related to this clinical trial should be kept in appropriate trial files. Records of patients, source documents, eCRFs, study drug inventory, and IRB and Sponsor correspondence pertaining to this trial must be kept on file. All trial documents must be kept secured for a period of 2 years after a marketing application is approved for CHS-388, or until 2 years after shipment and delivery of the study drug for investigational use is discontinued, or as long as required by local regulations, whichever is longer. There may be other circumstances for which the Sponsor is required to maintain trial records; therefore, the Sponsor should be contacted before removing or relocating trial records for any reason.

10.12. Publications

Publication by the clinical trial site(s) of any data from this trial must be carried out in accordance with the Clinical Trial Agreement.

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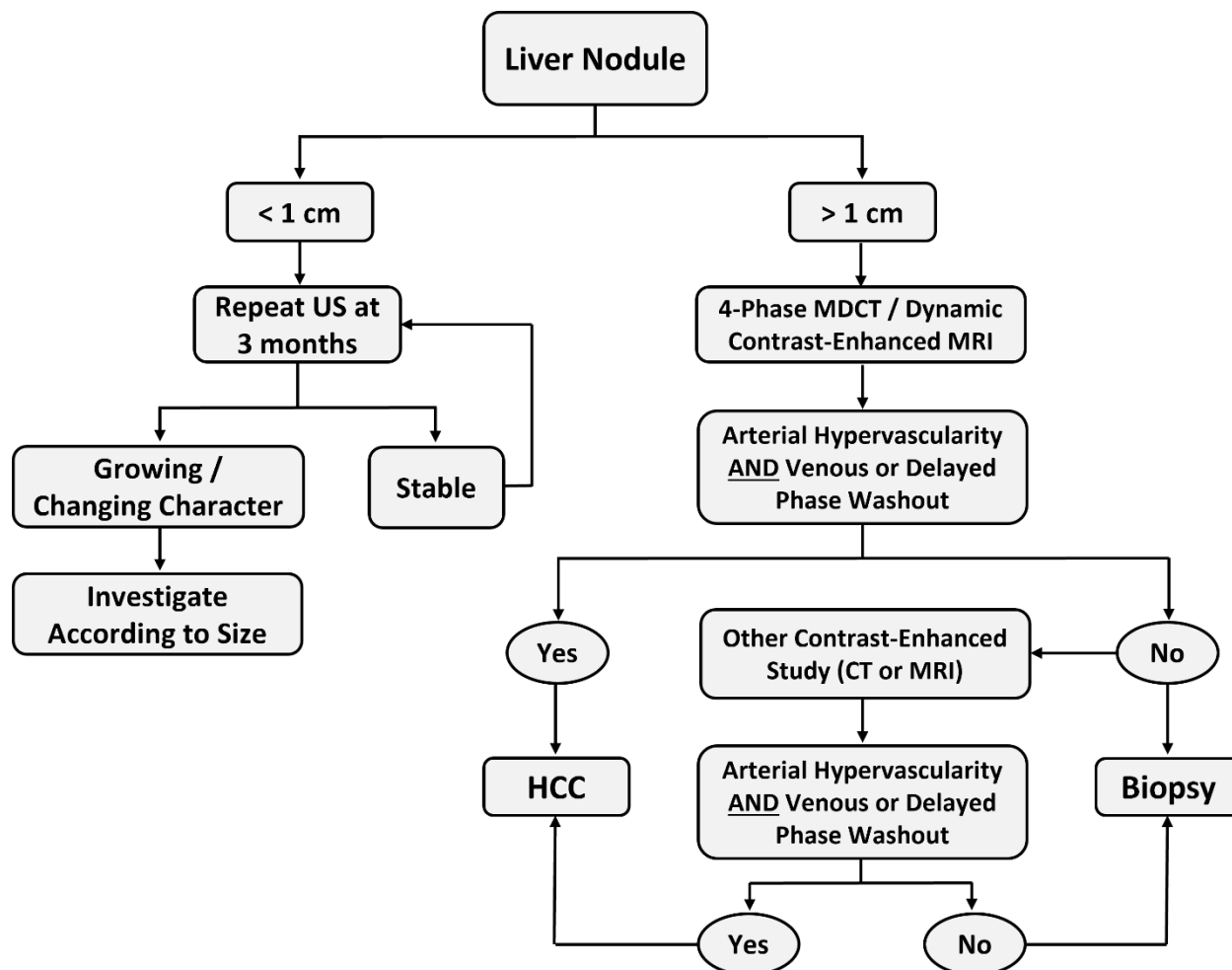
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APPENDIX 1. AASLD DIAGNOSTIC ALGORITHM FOR SUSPECTED HCC

Figure 7: AASLD algorithm for guidance on investigation of small nodules found on screening in patients at risk for HCC



Abbreviations: AASLD = American Association for the Study of Liver Diseases; CT = computed tomography; HCC = hepatocellular carcinoma; MDCT = multidetector CT; MRI = magnetic resonance imaging; US = ultrasound.

Source: Bruix and Sherman, 2011⁵⁷

APPENDIX 2. RESPONSE CRITERIA

Response Evaluation Criteria in Solid Tumors, version 1.1

**Table 31: Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
Lesion Response Criteria**

Evaluation of target lesions	
Complete response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to < 10 mm in short axis.
Partial response (PR)	$\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the Baseline sum of diameters.
Progressive disease (PD):	$\geq 20\%$ increase in the sum of diameters of target lesions from the smallest value on study (including Baseline, if that is the smallest). The sum of diameters must also demonstrate an absolute increase of ≥ 5 mm. Or the appearance of one or more lesions.
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Evaluation of nontarget lesions	
Complete response (CR)	Disappearance of all extranodal nontarget lesions, all lymph nodes must be non-pathological in size (< 10 mm in short axis), and, if applicable, normalization of tumor marker level.
Non-CR/Non-PD	Persistence of ≥ 1 nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive disease (PD)	Unequivocal progression of existing nontarget lesions. Or the appearance of one or more lesions.

Abbreviation: RECIST = Response Evaluation Criteria in Solid Tumors.

Source: Eisenhauer et al, 2009⁴⁵

Evaluation for target, nontarget, and new lesions are to be considered together to assess an overall response status at a time point as detailed in Table 32. For the overall response of CR or PR, confirmation of the response status at a subsequent time point at least 4 weeks (and a maximum of 9 weeks) apart from the initial observation (but not more than 9 weeks later) is recommended.

Table 32: Evaluation of Overall Response by Response Evaluation Criteria in Solid Tumors version 1.1

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response/remission, RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
Source: Eisenhauer et al, 2009⁴⁵

Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for Assessment of Response in HCC

In addition to RECIST v1.1 criteria, patients will also have response assessed by mRECIST.⁴⁶ mRECIST for HCC allows evaluation of treatment effects that are not reflected in simple total size changes of lesions and protects against premature assessment of progression based on benign changes due to cirrhosis and underestimation of response. Details are fully described in Lencioni and Llovet, 2010.⁴⁶ Extrahepatic lesion assessment as well as response categories and definitions are identical to RECIST v1.1. Key differences from RECIST v1.1 include the following:

- Lesions within the liver parenchyma are measured so as to include only the portion showing increased contrast enhancement in the arterial phase.
- New lesions in the liver must meet one of the following conditions to be considered indicators of progression:
 - ≥ 10 mm in longest diameter and showing typical HCC enhancement (enhancement during the arterial phase and washout during the portal venous phase).

- ≥ 10 mm in longest diameter with atypical enhancement but showing ≥ 10 mm of growth on a subsequent scan.
- Porta hepatis lymph nodes should never be selected as target lesions and should only be followed as nontarget lesions if their short axis measurement at Screening is ≥ 20 mm.

Optimal imaging for mRECIST is either by contrast-enhanced spiral CT, preferably with multislice scanners, or contrast-enhanced dynamic MRI. It is important to appropriately time the contrast administration to ensure high quality arterial phase imaging of the liver on the first run and high-quality portal venous phase imaging for the second run.⁴⁶

Target and nontarget lesions will be identified. Per Lencioni and Llovet,⁴⁶ to be selected as a target lesion for mRECIST, HCC lesions should meet the following criteria:

- The lesion can be classified as a RECIST measurable lesion (ie, the lesion can be accurately measured in ≥ 1 dimension as ≥ 1 cm).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI.

The following should be considered nontarget lesions:

- Lesions with ill-defined borders not suitable for accurate or repeat measurements should be considered nontarget lesions.
- Infiltrative-type HCC with unclear borders should be considered a nontarget lesion.
- Malignant portal vein thrombosis.
- Pleural effusions and ascites if cytologically proven. These fluid collections may be nonmalignant in the setting of concurrent cirrhosis and thus should only be used if cytologically proven to be malignant.

Table 33: Overall Response Assessments for mRECIST

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; IR = incomplete response; PD = progressive disease; PR = partial response/remission, mRECIST = modified Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Source: Table adapted from Lencioni and Llovet 2010.⁴⁶

Key differences between mRECIST and RECIST include the following:⁴⁶

- CR requires disappearance of any intratumoral arterial enhancement in all target lesions.
- PR and PD assessments are based on changes in the sum of the diameters of viable (enhancement in the arterial phase) target lesions.
- See Lencioni and Llovet 2010⁴⁶ recommendations on management of tumor necrosis, new liver lesions, ascites, and pleural effusions.

APPENDIX 3. CHILD-PUGH CLASSIFICATION OF SEVERITY OF CIRRHOSIS

Table 34: Child-Pugh Classification of Severity of Cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	None	Mild (easily controlled by medication)	Moderate to Severe (poorly controlled)
Bilirubin	< 2 mg/dL (< 34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	> 3 mg/dL (> 51.3 micromol/L)
Albumin	> 3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	< 2.8 g/dL (< 28 g/L)
INR Or Prothrombin time	< 1.7 < 4	1.7 to 2.3 4 to 6	> 2.3 > 6
Hepatic Encephalopathy	None	Grade I-II (mild or moderate)	Grade III-IV (severe to coma)

Abbreviations: INR = international normalized ratio.

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh Class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease). These classes correlate with 1- and 2-year patient survival: class A: 100% and 85%; class B: 80% and 60%; and class C: 45% and 35%.

Source: Pugh et al, 1973⁵⁸

APPENDIX 4. BARCELONA CLINIC LIVER CANCER (BCLC) CLASSIFICATION

Table 35: Barcelona Clinic Liver Cancer (BCLC) Classification

Stage		Defined as
A	Early	Single or up to 3 nodules < 3cm Preserved liver function ECOG PS 0
B	Intermediate	Multinodular Preserved liver function ECOG PS 0
C	Advanced	Portal invasion Extrahepatic spread: N1 or M1 Preserved liver function ECOG PS 1 to 2
D	Terminal	End-stage liver function ECOG PS 3 to 4

Abbreviations: ECOG = Eastern Cooperative Oncology Group; M = metastases; N = node; PS = performance status.

Source: Adapted from Llovet et al, 1999⁵⁹

APPENDIX 5. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Table 36: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al, 1982⁶⁰

APPENDIX 6. ANAPHYLAXIS PRECAUTIONS

Table 37: Anaphylaxis Precautions

Equipment Needed
• Tourniquet • Oxygen • Epinephrine for subcutaneous, IV, and/or endotracheal use in accordance with standard practice • Antihistamines • Corticosteroids • IV infusion solutions, tubing, catheters, and tape
Procedures
In the event of a suspected anaphylactic reaction during study treatment CCI the following procedures should be performed: 1. Stop the study drug CCI 2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb. 3. Maintain an adequate airway. 4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge. 5. Continue to observe the patient and document observations.

Abbreviation: CCI