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Date: 28 February 2023	Protocol No. CM-101-PSC-101	Version 4.0

CLINICAL STUDY PROTOCOL

A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL TRIAL EVALUATING THE SAFETY AND EFFICACY OF CM-101 IN SUBJECTS WITH PRIMARY SCLEROSING CHOLANGITIS (THE SPRING STUDY)

Protocol Number CM-101-PSC-101

Investigational Product CM-101

Phase 2a

US IND Number 157460

EudraCT Number 2019-002945-39

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Protocol Version 4.0

Protocol Date 28 February 2023

Confidentiality Statement

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This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

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DOCUMENT HISTORY

Document	Version Date	Version Number	Author
Original Protocol	10 Nov 2019	1.0	All
Protocol	20 Oct 2020	2.0	All clinical
Protocol	20 Dec 2020	2.0.1	All clinical
Protocol	07 Apr 2021	2.0.1G	All clinical
Protocol	23 Sep 2021	2.0.2EU	All clinical
Protocol	23 Sep 2021	2.0.2US	All clinical
Protocol	21 Nov 2021	2.0.3US	All clinical
Protocol	02 Aug 2022	3.0	All clinical
Protocol	28 Feb 2023	4.0	All clinical

SUMMARY OF CHANGES

Change	Rationale	Section(s)
Original Protocol Version 1.0 - 10 Nov 2019		
Protocol Version 2.0 - 20 Oct 2020		
Correction of typographical errors	Correction of typographical errors	Multiple
Stratification variables were updated	Addition of stratification according to presence or absence of Inflammatory Bowel Disease	Synopsis, 2.3, 8.2, 11.5
Inclusion criterion #6 was updated	Colonoscopy to be limited to subjects with ulcerative colitis only	Synopsis, 3.1
Exclusion criterion #4 was updated	Addition of a 12-month timeframe	Synopsis, 3.2
Exclusion criterion #8 was updated	Increase the excluded MELD score from ≥ 12 to ≥ 16 to facilitate patient recruitment	Synopsis, 3.2
Exclusion criterion #11 was updated	Raise in total bilirubin threshold from 2 to 3 ULN to reflect the higher levels found in study population	Synopsis, 3.2
Exclusion criterion #13 was updated	Raise in INR threshold from 1.3 to 1.5 to facilitate patient recruitment	Synopsis, 3.2

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Change	Rationale	Section(s)
Exclusion criterion #16 was changed to “Subjects with elevated Ca 19-9 value (> 129 U/mL) within 12 months prior to Screening, unless Ca 19-9 levels have been stable and clinical evaluation & repeated MRI imaging within the same time period has not provided evidence of cholangiocarcinoma.”	Reflects the fact that only patients with suspected or confirmed cholangiocarcinoma are to be excluded by this criterion.	Synopsis, 3.2
Exclusion criterion #28 was updated	Anti-HBc changed to HBSAg to exclude any active hepatitis B infection	Synopsis, 3.2
Addition of a blood draw for PK on Safety visit 3/EOS	To better evaluate the pharmacokinetics of CM-101	Synopsis, 4.10, 6.1
Requirement for 10h fast was removed for screening & SF2 visit	Not required since there is no lipid profile test in those visits	4.1, 4.7
Allowing liver enzymes baseline test to be done up to 3 days prior to randomization	To allow scheduling flexibility to study sites	4.1, 4.3
Addition of a Fatigue Severity Scale questionnaire at screening and treatment visits	To record changes in fatigue symptoms	4.1, 4.2, 4.4, 4.5, 4.7
Addition of CDAI and Partial Mayo scoring assessment for IBD patients	To assess changes in IBD scoring, if applicable	4.2, 4.5
Removal of requirement to perform pre-doses procedures within 2 hours prior to dosing	For specific procedures which are time-limited there is already a disclaimer mentioning that these must be done within 90 min prior to dosing	4.2, 4.5
Allowing use of weight measurement form last visit for dose calculation	Applicable in case the prescription is sent to the pharmacy prior to subject weight measurement	4.2, 4.5
Addition of wording forbidding the use of a same IV line for drug administration and PK blood draws	To avoid contamination, dilution, phlebotomy	4.2, 4.5
Post-dose fasting requirements updated	Requirement to fast only one-hour post-dose	4.2, 4.5
Safety phone calls updated	Addition of review of concomitant medications	4.3, 4.6
Requirement to use the same Transient Elastography device model as during screening	To ensure consistency of assessment’s results and avoid inter-device variability	4.7
Addition of whole blood sampling for immune cell sub populations evaluation at visit 3	To better evaluate the immune cell sub populations	4.7
Safety Follow-up updated	Addition of ± 3 & ± 7 days window to follow-up phone call (Study Day 147) & to Safety Visit 3 (Study Day 189), respectively	4.9, 4.10

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Change	Rationale	Section(s)
Conversion of the last follow-up phone call (Study Day 189) to safety visit 3	To better evaluate the safety and allow blood sampling for anti-CM-101 antibody (ADA)	4.10
Addition of blood sampling for anti-CM-101 antibody (ADA) at visit 3 and at end of study visit (safety visit 3)	To better evaluate the development of anti-drug antibodies (ADA) following repeated administrations of CM-101	4.7, 4.10
Change of timing for prohibition of investigational agents, other than CM-101	Change from 12 weeks to 60 days for consistency with exclusion criterion 34 and section 3.2	9.1
Change of timing for prohibited antibiotics	Change from 12 weeks to 90 days for consistency with exclusion criterion 22	9.1
Addition of possibility of home or off-site visits for safety visits 1&3 and study visits 2 to 5	Mitigation measure in the context of the COVID-19 pandemic	4.11
Safety reporting updated	After study safety visit 2/EOT(Study Day 105) up until study safety visit 3/EOS (Study Day 189), only serious adverse events will be recorded and reported ongoing adverse events will be reviewed.	5, 10.1, 10.6
Study flowchart and schedule of activities updated	To reflect the relevant above-mentioned changes	Appendix A
Urinalysis parameters updated	Urinalysis to be performed either via lab-based test or dipstick to allow flexibility	Appendix A & B
Serum biochemistry parameters updates	Urea to be measured either via BUN or serum urea to allow flexibility	Appendix B
Protocol Version 2.0.1 - 20 Dec 2020		
Safety reporting updated	After study safety visit 2/EOT (Study Day 105) up until study safety visit 3/EOS (Study Day 189), all AEs will be recorded, as requested by the Medicines and Healthcare Products Regulatory Agency	5, 10.1
Safety follow up call (Study Day 147) and Safety visit 3/EOS visit (Study Day 189) update	To reflect the relevant above-mentioned changes	4.9, 4.10
Study flowchart and schedule of activities updated	To reflect the relevant above-mentioned changes	Appendix A
Protocol Version 2.0.1G - 07 Apr 2021 (for Germany only)		
Addition of EudraCT number 2019-002945-39	Mandatory requirement by Germany RA	1 st page
Protocol Version 2.0.2EU, 2.0.2US - 23 Sep 2021 (for European Union [EU] countries and United States [US])		

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Change	Rationale	Section(s)
Amendment of the contraception methods	To reflect CTFG contraception recommendations considered as highly effective	Synopsis, 3.1, 9.2
Correction of deletion error	Whole blood samples to be limited to selected countries/sites	6.2, Appendix A
Protocol Version 2.0.3US - 21 Nov 2021		
Addition of instruction for the management of drug induced liver injury (DILI)	Provide Investigators with guidelines for the assessment, monitoring, and criteria for drug interruption in potential DILI cases	3.4, 10.8
Version 3.0 - 02 Aug 2022		
Correction of typographical errors, formatting, references, and revised protocol version and date	Correction of typographical errors, document formatting, and protocol version	Global
Rationale for Dose Selection was updated	To provide justification for a 20 mg/kg dose cohort and duration of treatment for the open label treatment period.	1.3.2
Study objectives and endpoints were changed	To better align with the purpose of the study, which is to primarily assess safety and tolerability of CM-101	Synopsis, 2.1, 2.2
Study design was revised to add 2 dose cohorts of 5 mg/kg and 20 mg/kg.	Dose cohorts were added to better assess the safety, tolerability, PK, and PD of CM-101 based on PK modeling.	Synopsis, 3.1, 3.2, 7.1, 7.2
Study sample size was updated to reflect additional dose cohorts.	To reflect the above-mentioned additional dose cohorts, resulting in a change from 45 subjects to 93 subjects.	Synopsis, 3.1, 3.2, 7.1, 7.2, 10.1
Study design was revised to add a 33-week (11 dose administrations) open label (OL) treatment period was added. Overall study duration was therefore revised.	An OL treatment period was added to further evaluate CM-101 at doses of 10 or 20 mg/kg. Overall study duration therefore increased to 69 weeks from 31 weeks.	Synopsis, 3.1, 3.3
Overall study duration, Screening Period, and DB treatment period were revised	Screening period changed to 42 days, and DB treatment period was updated to 15 weeks from 12 weeks to reflect Q3W dosing. Overall study duration was therefore revised.	Synopsis, 3.1, 3.3, 4, 4.5,
Stratification was removed	Stratification was removed due to updated randomization plan and sample size.	Synopsis, 3.1, 7.2, 7.2.1, 10.4.1, 10.4.2

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Change	Rationale	Section(s)
Study visits, procedures, and assessments were added and revised to reflect addition of OL treatment period.	Changes were made throughout the protocol to reflect the revised study design and addition of the OL treatment period.	Multiple
Inclusion criterion #2 was updated	Clarified subjects would be eligible if cholangiography was performed within 24 weeks prior to randomization but subject has clinical evidence of large duct PSC for more than 24 weeks duration.	Synopsis, 4.1
Inclusion criterion #4 was updated	Removed requirement for Baseline serum ALP assessment	Synopsis, 4.1
Inclusion criterion #5 was updated	Revised requirement for stable UDCA dosing for ≥ 12 weeks prior to Screening rather than at randomization.	Synopsis, 4.1
Inclusion criterion #6 was updated	Clarified concomitant IBD criteria and added eligibility for subjects with a history of colectomy.	Synopsis, 4.1
Inclusion criterion #7 was updated	Clarified concomitant medication was referring to therapies for PSC	Synopsis, 4.1
Inclusion criterion #11 was added	Fenofibrates and other fibrates are allowed to facilitate patient recruitment	Synopsis, 4.1
Exclusion criterion #6 was updated	Clarification was added to specify liver biopsy staging will be used should a fibrosis staging discrepancy arise between liver biopsy staging and transient elastography results.	Synopsis, 4.2
Exclusion criterion #9 was updated	Removed requirement for AST and ALT assessments at randomization.	Synopsis, 4.2
Exclusion criterion #10 was updated	Update to reflect removal of ALP, AST, and ALT assessments at baseline and randomization.	Synopsis, 4.2
Exclusion criterion #11 was updated	Removed optional total bilirubin assessment at randomization. Total bilirubin will be assessed at Screening to determine eligibility.	Synopsis, 4.2
Exclusion criterion #25 was updated	Clarified subjects not on a stable dose of fenofibrate or other fibrates as defined in Inclusion criterion #11 will be excluded.	Synopsis, 4.2
Exclusion criterion #32 was updated	Added clarification that COVID-19 vaccines and killed (inactivated) vaccines are allowed during the study.	Synopsis, 4.2

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Change	Rationale	Section(s)
Subject withdrawal criteria section was added and revised.	Subject withdrawal criteria section was added and clarified study treatment discontinuation, study withdrawal, and study stopping.	Section 4.4, 4.4.1-4.4.4, 4.7
Eligibility for OL treatment period section was added	To provide eligibility conditions for the OL treatment period.	4.6
COVID-19 vaccination was added to permitted recent vaccines.	To reflect allowance of COVID-19 vaccination during the study.	Synopsis, 4.1, 8.1.2
Use of fenofibrates and other fibrates was changed to be allowed in the study	Allowance of fenofibrates and other fibrates was revised from prohibited to be allowed as long as subjects have been on a stable dose for ≥ 24 weeks and plan to be on a stable dose for duration of DB treatment period.	Synopsis, 4.1, 4.2, 8.2, 8.3, 8.4
Additional study restrictions were revised.	Restriction of strenuous physical exercise was removed, and time of direct clinical supervision following study drug administration was changed from 1 hour to 2 hours.	8.4
Twelve-week (12W) analysis set was revised to fifteen-week (15W) analysis set.	To reflect a 15-week treatment coverage rather than 12 weeks in the DB treatment period	Synopsis, 10.2
Statistical analyses were updated	To reflect changes in primary, secondary, and exploratory endpoints, dose cohorts, and treatment periods.	Synopsis, 10.4, 10.4.1-10.4.4
Addition of 2 interim analyses (IAs) for 3 total IAs	Two IAs were added. Timing, triggers, and analyses evaluated are described for all 3 IAs.	Synopsis, 10.5
Study completion was updated	Study completion was updated to conclude after all enrolled subjects complete the EOS visit rather than after completion of the SF2/EOT visit.	13.4
Schedule of assessments updated	To reflect the relevant above-mentioned changes	Appendix 1
Table of laboratory parameters was updated	To clarify which laboratory parameters will be performed locally and centrally	Appendix 2
Version 4.0 – 28 Feb 2023		
Sponsor Medical Monitor was updated		Title Page
Sponsor Representative was updated		Protocol Signature Page

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Change	Rationale	Section(s)
The study design was revised to remove the 5 mg/kg dose cohort	Lower dose cohort of 5mg/kg removed based on adequate number of subjects exposed to lower dose in other studies and to support overall study enrollment timing	Synopsis, 1.3.1, 1.3.2, 1.4, 3.1, 7.1.1, 7.5, 10.1
Study sample size was updated to reflect removal of a dose cohort	To reflect the above-mentioned removed dose cohort, resulting in a change from 93 to 68 subjects	Synopsis, 3.1, 3.2, 10.1
Number of subjects expected to receive CM-101 was updated to reflect removal of a dose cohort	To reflect the above-mentioned removed dose cohort, resulting in a change from 75 to 50 subjects	Synopsis, 3.1, 7.1.1, 10.1
Active-to-placebo ratio was updated to 5:2	To reflect the above-mentioned removed dose cohort and subject numbers	Synopsis, 3.1, 7.1.1, 7.2
Data and Safety Monitoring Board (DSMB) was revised to DMC	Updated to correlate with the DMC charter	Global
Study duration description was revised	Changed references to “DB” to “Open-label Treatment Period”. Study duration is now up to 33 weeks for subjects not participating in the Open-label Treatment Period. Follow-up Period for the Open-label Treatment Period updated to 12 weeks starting at the SF2/EOT Visit (Day 336) and ending at the SF3/EOS Visit (Day 420)	Synopsis, 3.3, Appendix 1
Inclusion criterion 6 was revised	Clarified that concomitant inflammatory bowel disease is allowed but not required and must meet stability criteria. Added part c to indicate that medication should be stable for ≥ 12 weeks prior to Screening and planned to remain stable during the DB portion of the study	Synopsis, 4.1
Inclusion criterion 7 was revised	Concomitant medication for PSC must be planned to remain stable during the DB portion of the study	Synopsis, 4.1
Exclusion criterion 6 was revised	Redefined recent liver biopsy as ≤ 12 months	Synopsis, 4.2
Exclusion criterion 22 was revised	Clarified known acute cholangitis and specify time window for treatment with antibiotics	Synopsis, 4.2
Exclusion criterion 23 was revised	Patients taking biologics may now participate in the study if dose is stable	Synopsis, 4.2

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Change	Rationale	Section(s)
Exclusion criterion 24 was removed	Biologics are no longer a prohibited concomitant medication, patients taking biologics may now participate in the study	Synopsis, 4.2
The interim analysis plan was revised	Removed interim analysis after 5 mg/kg cohort has completed Week 15 visit	Synopsis, 10.5
Efficacy analysis plan was revised	Removed “with alpha = 0.05”	Synopsis, 10.4.2
The description of treatment of missing values was removed	Removed from protocol to be specified in SAP.	Synopsis, 10.3, 10.4.2
Frequency of DMC meetings was revised	Updated to correlate with the DMC charter	3.1, 9.11
Subject identification scheme was revised	Removed replacement subjects	4.3
Subject withdrawal section was revised	Clarified that subjects may be withdrawn for safety reasons based on Investigator judgement	4.4
Discontinuation of study treatment section was revised	Moved reference to subjects who completed Screening but were not dosed within 42 days to appropriate section	4.4.1, 4.5
Re-screening of subjects section was revised	Removed subject replacement. Added definition of and reporting requirements for screen failures. Clarified process for re-screening screen failures.	4.5
Eligibility for Open-label Treatment Period was revised	Removed additional conditions	4.6
Re-Screening removed from Screening Visit description	Removed reference to Re-Screening in the Screening Visit	5.1.1
Pre-Dose assessments and procedures lists for Visits 1 and Visits 2-5 were revised	Revised to remove duplicates and match Appendix 1	5.1.2.1, 5.1.2.4
Safety Visit 1, Visit 6, and Visit 17 activities lists were revised	Revised to match Appendix 1	5.1.2.3, 5.1.2.5, 5.1.3.3
Pre-Dose assessments and procedures lists for Visits 7-10 and 12-16 and Visit 11 were revised	Revised to remove duplicates and match Appendix 1	5.1.3.1, 5.1.3.2
Pregnancy Test description was revised	Added link to section 8.5	5.2.8
Pharmacodynamic, Fibrosis, and Inflammatory Marker Assessments section was revised	Clarified PD and inflammatory biomarkers	5.3.2
Blinding section was revised	Specified that drug supply personnel may be unblinded and that Sponsor will have unblinded personnel	7.3

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Change	Rationale	Section(s)
Breaking the blind section was revised	Updated since DMC does not have access to IWRS or unblinding as referenced in this section	7.4
Prior medications definition was revised	Definition updated for clarity	8.1
Prohibited medications list was revised	Removed biologics, amoxicillin/clavulanate (Augmentin), and vancomycin from prohibited medications list	8.2
Allowed medication section was revised	Added Vancomycin as treatment for PSC is allowed if stable for ≥ 12 weeks before screening.	8.3
DMC description was revised	Updated to correlate with the DMC charter: DMC composition, blinded review, and documentation of unblinded data reviews.	9.11
Statistical analysis description was revised	All tests will be two-tailed, with a significance level of 5%.	10,4
Sample size consideration was revised	Alpha set to 0.025 to adjust type 1 error inflation, power updated to 81%	Synopsis, 10.1
Table 8 footnotes 23 and 24, and Table 9 footnotes 20 and 21 were revised	Added list of serum inflammatory markers	Appendix 1
Local and Central Laboratory tables were revised	Updated for clarity: Urine/serum pregnancy test added, Serum Bile Acids and C4 description added, updated description of ELF	Appendix 2

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C4 = 7 α -hydroxy-4-cholesten-3-one; CDAI = Crohn's Disease Activity Index; COVID-19 = coronavirus disease 2019; CTFG = Clinical Trials Facilitation and Coordination Group; DB = double-blind; DMC = Data Monitoring Committee; ELF = enhanced liver fibrosis; EOS = end of study; EOT = end of treatment; HBSAg = hepatitis B surface antigen; IBD = inflammatory bowel disease; INR = international normalized ratio; IV = intravenous; IWRS = interactive web response system; MELD = model for end-stage liver disease; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PSC = primary sclerosing cholangitis; Q3W = once every three weeks; RA = regulatory authority; SAP = statistical analysis plan; SF = safety visit; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

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PROTOCOL SIGNATURE PAGE

Protocol Title A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Clinical Trial Evaluating the Safety and Efficacy of CM-101 in Subjects with Primary Sclerosing Cholangitis (The SPRING Study)

Protocol Identification CM-101-PSC-101

Study Phase 2a

Sponsor Chemomab Ltd., Israel

Sponsor Representative

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Council for Harmonisation (ICH), and Good Clinical Practice (GCP) guidelines and applicable local regulations.

DocuSigned by:



Chief Medical Officer

28 February 2023
Date

Principal Investigator

By signing below, I, the Investigator, approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, electronic case report form (eCRF) and any protocol-related documents (subject to any amendments agreed to in writing between the Sponsor and Principal Investigator). I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Chemomab Ltd. I understand that the study may be terminated, or enrollment suspended at any time by Sponsor, or by me, at my center, if it becomes necessary in my opinion, to protect the best interests of the study subjects.

Name	Investigator Signature	Date
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Center Name	City, Country
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PROTOCOL SYNOPSIS

Study Title	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Clinical Trial Evaluating the Safety and Efficacy of CM-101 in Subjects with Primary Sclerosing Cholangitis (The SPRING Study)
Protocol No.	CM-101-PSC-101
Planned Number of Trial Sites	A total of 68 subjects are planned to enroll at approximately 75 sites.
Study Phase	2a
Study Objectives	Primary Objective: The primary objective of this study is to determine the safety and tolerability of multiple dose levels of the anti-human CCL24 monoclonal antibody CM-101 in adult subjects with Primary Sclerosing Cholangitis (PSC). Secondary Objectives: Secondary objectives include evaluation of the activity of CM-101 as measured by a decrease in serum alkaline phosphatase (ALP) levels and reductions in enhanced liver fibrosis (ELF) scores, clinical biochemistry response to treatment (liver enzyme levels and lipid profile), CM-101 pharmacokinetics (PK), pharmacodynamic (PD) measures, and immunogenicity (anti-drug antibodies [ADA]). Exploratory Objectives: Exploratory objectives include evaluating the effect of CM-101 administration to subjects with PSC on liver stiffness, and serum inflammatory and fibrotic markers, as well as other PD parameters. In addition, target engagement by measurement of serum CCL24 levels will be evaluated.
Study Endpoints	Primary Endpoints: This study has multiple safety-related endpoints including the frequency and severity of treatment-emergent AEs (TEAEs), changes in vital signs, changes in clinical safety laboratories, and evaluation of infusion site reactions over the 15-week double-blind (DB) treatment period. Secondary Endpoints: 1. Safety-related endpoints include the frequency and severity of TEAEs, changes in vital signs, changes in clinical safety laboratories, and evaluation of infusion site reactions over the 48-week DB and open-label (OL) treatment periods. 2. Change from baseline through Week 15 in serum ALP levels by treatment cohort 3. Change from baseline through Week 15 in ELF score by treatment cohort 4. Change from baseline through Week 15 in ALP response rates, defined as reduction of ALP to $1.3 \times$ upper limit of normal (ULN), or a combination of ALP reduction to $1.5\text{--}1.3 \times$ ULN with an at least 40% reduction 5. Percent change from baseline through Week 15 in liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transferase [GGT])

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	6. Change from baseline through Week 15 in liver fibrosis markers as measured by pro-peptide of type III collagen (PRO-C3) and pro-peptide of type v collagen (PRO-C5) 7. Elucidation of the serum PK profile of repeated administrations of CM-101 8. Evaluation of the development of ADA following repeated administrations of CM-101 over a 15 and 48-week period. Exploratory: 1. The effect of repeated administrations of CM-101 on the CM-101 target (CCL24) and on other relevant cytokines and chemokines. 2. Change over time in serum inflammatory markers as measured by high-sensitivity C-reactive protein (hsCRP), monocyte chemoattractant protein 1 (MCP1), interleukin (IL)-6, regulated on activation, normal T cell expressed and secreted (RANTES), and IL-1 3. Change from baseline through Week 15 in liver stiffness using Transient Elastography (preferably Fibroscan™) 4. Change from baseline through Week 15 in ELF response defined as a reduction of ≥ 0.5 in ELF score 5. Change from baseline through Week 48 on serum ALP, ELF, liver enzymes, liver fibrosis markers, serum inflammatory markers, and liver elastography Additional evaluations of cytokines and inflammatory and fibrotic markers may be conducted using blood tests collected during the study.
Study Design	This is a Phase 2a, randomized, double-blind, placebo-controlled, multiple-dose, cohort-based study evaluating the safety and efficacy of CM-101 in subjects with PSC as their predominant disease. Up to 68 subjects who provide written informed consent and meet all of the inclusion and none of the exclusion criteria will be randomized to receive either CM-101 (N=50 subjects) at doses of 10 mg/kg or 20 mg/kg (25 subjects in each CM-101 dose level) or matching placebo (N=18 subjects) in approximately 5:2 active-to-placebo ratio. Randomization of placebo subjects will be blocked to ensure that 9 placebo subjects are enrolled into each dose cohort (10 and 20 mg/kg). Study drug, defined as CM-101 or placebo, will be administered as an intravenous (IV) infusion given over 60 minutes (± 5 minutes). The investigational product (IP) is defined as CM-101. Enrollment into each CM-101 dose level cohort will be done sequentially. Subjects will be randomized into the 10 mg/kg dose cohort (N=25) followed by the 20 mg/kg dose cohort (N=25). The initiation of the 20 mg/kg dose cohort will occur only after a review of all available safety and tolerability data from a planned interim analysis of the study is completed, and advancement to this higher dose level is recommended by the CM-101 Data Monitoring Committee (DMC). This study will consist of a screening period, DB treatment period, OL treatment period, and safety follow-up period. The timing of study visits, study assessments, and associated time windows are presented in the Schedule of Assessments (SOA; Appendix 1). The study design schematic is depicted in Figure 1. Prior to any Screening Visit assessments, subjects will be consented into the study and sign the Informed Consent Form (ICF). Subjects will be screened for eligibility and consented during the Screening period up to 42 days prior to study drug administration.

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	Subjects not meeting Inclusion/Exclusion criteria for entry in the study will not be eligible for the study and may be screened up to one additional time as detailed in Section 4.5. During the DB treatment period, subjects will receive 5 total dose administrations of study drug (IP or placebo) once every 3 weeks (Q3W) for a coverage of 15 weeks. After completing the DB treatment period, subjects may elect to enroll in an OL treatment period. In the OL treatment period, subjects will receive a dose of IP Q3W for 11 administrations for a coverage of 33 weeks, resulting in a combined total coverage of up to 48 weeks. Subjects who do not elect to continue treatment in the OL dosing period will undergo an End of Treatment (EOT)-DB visit at Week 15 (Day 105), a Safety Follow-up Call at Week 21 (Day 147), and an End of Study (EOS) visit at Week 27. Eligible subjects who continue treatment in the OL treatment period will receive CM-101 at either a 10 mg/kg or 20 mg/kg dose commencing at Week 15 (OL Treatment 1), and the subjects will undergo an EOT-OL visit at Week 48 (Day 336), a Safety Follow-up Call at Week 54 (Day 378), and an EOS visit at Week 60 (Day 420). Male and female adults, ages 18 to 75 inclusive, with PSC and a serum ALP of at least $1.5 \times \text{ULN}$ will be included in this study. Eligibility will be based on a diagnosis of large duct PSC of more than 24 weeks' duration based on chronic cholestatic liver biochemistry alongside consistent cholangiography, and the absence of secondary etiologies. Subjects with small duct PSC without large duct PSC will not be enrolled. Subjects must have no new clinical concern of cholangiocarcinoma within the last 12 months prior to randomization. All participating subjects will have a transabdominal ultrasound done as part of the Screening procedures. Subjects with ulcerative colitis are eligible for recruitment with a Partial Mayo score of ≤ 3 with no individual sub-score exceeding 1 point. Subjects with ulcerative colitis must have undergone colonoscopy with biopsy confirming no dysplasia or colorectal cancer within 18 months of randomization, and no history of colectomy (at any time). Subjects with Crohn's Disease must be in remission defined as a Crohn's Disease Activity Index (CDAI) < 150. Subjects on treatment with ursodeoxycholic acid (UDCA) therapy must be treated at a stable dose not greater than 23 mg/kg per day for at least 12 weeks prior to screening. Subjects receiving other concomitant medications need to be on stable therapy for at least 12 weeks prior to the first study treatment day (randomization). Regardless of treatment period, all study drug administrations will be done in the clinical research facility (i.e., under observation of study staff however the study does not involve hospitalization). Subjects will remain under medical observation for 2 hours post dosing for all administrations in both DB and OL treatment periods, unless either a reaction to the study drug administration occurs, or in the Investigator's judgment, the subject's safety warrants a longer observation post dosing during a specific visit. Subjects will be contacted by phone 3 days following each study drug administration visit (Treatments 1-5). In addition, following the first study drug administration, a safety visit will take place 7 days after the study drug administration date (Safety Visit 1; SF1). During the study, blood testing will be done for safety laboratory evaluations, liver enzyme measurements, lipid profiles, ADA, PK, and PD analyses. In addition, liver fibrosis markers (e.g., ELF Blood Test, PRO-C3, and PRO-C5), serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES, and IL-1), and other relevant cytokines
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	and chemokines will be evaluated. Changes in liver stiffness will be evaluated using Transient Elastography (preferably Fibroscan). Fatigue will be assessed at each treatment visit and Safety Visit 2 (SF2)/EOT using a Fatigue Severity Scale questionnaire. The detailed time points for study assessments are described in Section 5 and in Appendix 1).
Investigational Product	
Dosage and Regimen of Administration	<u>Double-blind Treatment Period</u> Study Drug Administration: CM-101 at doses of 10 and 20 mg/kg or matching placebo will be administered Q3W for 5 treatments (for a total coverage of a 15-week treatment period). <u>Open-label Treatment Period</u> Investigational Product Administration: CM-101 at doses of 10 and 20 mg/kg will be administered Q3W for 11 administrations for a total coverage of 33 weeks in the OL treatment period, resulting in a combined 48-week treatment period for subjects on CM-101 during the DB period and a 33-week treatment period for subjects on placebo during the DB period.
Reference Therapy	
Study Procedures	The study will be comprised of a screening period, double-blind and open-label treatment periods, and a follow-up period. The detailed study procedures are described in Section 5 and in the SOA (Appendix 1).
Study Duration	Study duration for each participating subject will be up to 66 weeks (up to 33 weeks for patients not entering the Open-label Treatment Period) as follows: • Screening Period: Up to 42 days (6 weeks) prior to randomization • Double-blind Treatment Period: 15 weeks; CM-101 or placebo will be given as IV infusion Q3W for 5 administrations • Open-label Treatment Period: 33 weeks; CM-101 treatment will be given as IV infusion Q3W for 11 administrations • Follow-up Period: 12 weeks starting at the SF2/EOT Visit (Day 336) and ending at the SF3/EOS Visit (Day 420)
Sample Size and Target Population	A total of 68 adult subjects (age 18-75 years, inclusive) with PSC will be enrolled to the study and randomized to receive either CM-101 (N=50 subjects) at doses of 10 mg/kg or 20 mg/kg or matching placebo (N=18). As the primary outcome measure for this trial is safety, no formal power analyses have been applied. Each dose cohort group size, and thus the overall sample size for the study, is sufficiently large to provide meaningful assessments of the safety and tolerability of each planned CM-101 dose and is consistent with first-in-patient safety and efficacy trials in PSC. With respect to the secondary outcome measure of relative change from baseline in serum ALP for CM-101 treatment

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	groups compared with placebo and based on two 2-sided independent samples t Tests at an alpha level of 0.025 (to adjust the type 1 error inflation), the planned cohort size of 25 subjects in each CM-101 dose group and placebo cohort size of 18 subjects will provide approximately 81% statistical power to detect a 20% change with a matching 20% standard deviation.
Inclusion Criteria	Subjects must meet all inclusion criteria to be eligible for the study: 1. Males and females, age 18 to 75 years, inclusive. 2. Diagnosis of large duct PSC (intrahepatic and/or extrahepatic) of more than 24 weeks' duration (defined as cholestatic serum liver tests with consistent magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography showing sclerosing cholangitis once secondary causes of sclerosing cholangitis have been excluded). Note: Subjects must have cholangiographic changes showing sclerosing cholangitis in order to be eligible for the study. Subjects will be eligible if cholangiography has been performed within 24 weeks prior to randomization but there is clinical evidence of large duct PSC for more than 24 weeks' duration. 3. No significant clinical concern for cholangiocarcinoma based on clinical, laboratory, or imaging findings in the 12 months preceding randomization. Note: All subjects will have a transabdominal ultrasound done as part of the screening procedures. 4. Serum ALP greater than $1.5 \times \text{ULN}$ in Screening blood tests. 5. Subjects receiving UDCA must receive a stable dose for ≥ 12 weeks prior to Screening and must not exceed 23 mg/kg/day during this time. 6. Concomitant inflammatory bowel disease (IBD) is allowed, but not required, and must meet the following stability criteria: a. Subjects with ulcerative colitis: i. Must either be in remission or have mild disease. Remission is defined as a Partial Mayo score of ≤ 2 with no individual sub-score exceeding 1 point. Mild disease is defined as a Partial Mayo score of ≤ 3 with no individual sub-score exceeding 1 point. ii. Must have undergone colonoscopy with biopsy confirming no dysplasia or colorectal cancer within 18 months of randomization, and no history of colectomy (at any time). b. Subjects with Crohn's Disease must be in remission as defined by a CDAI < 150. c. If receiving concomitant medication for their IBD, dose must be stable for ≥ 12 weeks prior to screening and dose should remain stable during the DB portion of the study. 7. Subjects receiving concomitant medications for their PSC must be on stable therapy for ≥ 12 weeks prior to randomization and plan to remain on that stable dose during the DB portion of the study. 8. Female subjects of childbearing potential (defined as sexually mature women who have not undergone surgical sterilization or who have not been naturally postmenopausal for at least 24 consecutive months for women ≤ 55 years; for

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	women > 55 years 12 consecutive months) must have a negative serum pregnancy test prior to starting study treatment. Sexually active women of childbearing potential must agree to use a highly effective method of contraception from the Screening Visit throughout the study period including 18 weeks post last dose. See Section 8.5 for acceptable methods of contraception. 9. Male subjects, if not vasectomized, must agree to use barrier contraception (condom plus spermicide) during heterosexual intercourse from screening through to study completion and for 90 days from the last dose of study investigational medicinal product. 10. Subjects must be able to understand and provide a signed, written ICF. 11. Subjects receiving fenofibrate or other fibrates must be on a stable dose for ≥ 24 weeks prior to Screening and plan to remain on that stable dose during the DB portion of the study.
Exclusion Criteria	The clinically predominant disease must be PSC. Therefore, subjects must not meet any exclusion criteria to be eligible for the study: - Subjects with presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations. - Subjects with presence of competing etiology of liver disease (including, but not limited to, viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, IgG4-associated cholangitis, primary biliary cholangitis, etc.) are excluded from the study. Subjects with possible overlap syndrome with autoimmune hepatitis are excluded if the Investigator considers autoimmune hepatitis as the predominant liver injury. - Subjects with small duct PSC in the absence of large duct disease. - Subjects with percutaneous biliary drain or bile duct stent or subjects who had required biliary drainage within 12 weeks of Screening. - Subjects that have undergone prior biliary surgery (laparoscopic or open surgery) other than those who at the time of screening are more than 6 weeks after cholecystectomy without surgical complications. - Subjects with evidence of cirrhosis, as determined by local transient elastography (preferably Fibroscan) values of ≥ 14.4 kPa obtained during the Screening period. In case of a fibrosis staging discrepancy between a recent (≤ 12 months) liver biopsy staging and the transient elastography results, eligibility will be based on the liver biopsy staging. - History of cirrhosis and/or hepatic impairment (Child-Pugh classes A, B, and C), and/or hepatic decompensation including ascites, encephalopathy, or variceal bleeding. - Subjects who have undergone or are planned for liver transplantation or with current model of end stage liver disease (MELD) score ≥ 16. - Subjects with AST or ALT values $> 5 \times$ ULN as determined at Screening.

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	10. Subjects who show ‘clinically significant’ lab changes (as judged by the Investigator) at Screening will be excluded. 11. Subjects with serum total bilirubin values $> 3 \times \text{ULN}$ at Screening. 12. Subjects with known Gilbert’s syndrome or a history of elevations in unconjugated (indirect) bilirubin $> \text{ULN}$. 13. Subjects with International Normalized Ratio (INR) > 1.5 which does not correct on vitamin K replacement, in the absence of anticoagulants. 14. Subjects with serum creatinine $> 1.4 \text{ mg/dL}$ ($123 \mu\text{mol/L}$) and/or a platelet count $< 100 \times 10^9/\text{L}$ 15. Subjects with history of cholangiocarcinoma or a high clinical suspicion of cholangiocarcinoma, as indicated by clinical presentation, laboratory tests or imaging of a functional dominant stricture. 16. Subjects with elevated cancer antigen 19-9 (Ca 19-9) value ($> 129 \text{ U/mL}$) within 12 months prior to Screening unless Ca 19-9 levels have been stable and clinical evaluation and repeated magnetic resonance imaging (MRI) within the same time period has not provided evidence of cholangiocarcinoma. 17. Subjects with a prior biliary stricture necessitating intervention should be stable for ≥ 24 weeks prior to randomization without intervention, or episode of cholangitis, and should show a low level of clinical suspicion of cholangiocarcinoma. 18. Subjects with current known portal hypertension with complications, including known gastric or large esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds, or related therapeutic or prophylactic interventions (e.g., beta blockers, insertion of variceal bands or transjugular intrahepatic portosystemic shunt). 19. Subjects with active malignancy (diagnosed and/or treated within 3 years of randomization), other than: a. adequately treated non-metastatic basal cell skin cancer; b. squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to randomization; c. history of cervical carcinoma in situ that has been adequately treated and that has not recurred. Note: subjects with history of malignancy (i.e., > 3 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the Sponsor or Medical Monitor on a case-by-case basis prior to randomization. 20. Subjects with a ‘clinically significant’ (as judged by the Investigator) unexplained weight loss during the 24 weeks prior to randomization. 21. Subjects showing deleterious effects of alcohol abuse (as assessed by the Investigator) or that consume excessive amounts of alcohol (> 14 units/week for both females and males; for the purposes of this study one unit of alcohol is considered to be equal to 8 gr). 22. Subjects with known or suspected acute cholangitis in the 90 days prior to randomization, including cholangitis treated with antibiotics within the 90 days.
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	23. Subjects experiencing flare in colitis activity within 90 days of randomization requiring intensification of therapy beyond baseline maintenance treatment or use of oral prednisone > 10 mg/day (or equivalent), start or dose change of biologics ≤ 12 weeks before screening and or hospitalization for colitis within 90 days of randomization. 24. <i>[Note EC removed in v4.0]</i> 25. Subjects treated with or who are expected to begin treatment with fenofibrate or other fibrates or subjects who had a change in dose within 24 weeks of Screening, or subjects who are not planned to remain on a stable dose throughout the DB portion of the study. 26. Subjects that use any prohibited medication as described in Section 8.2. 27. Subjects who have a known history of hypersensitivity reaction to CHO-derived antibodies, CM-101, or any of the formulation excipients. 28. Subjects with known chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or that have positive hepatitis B surface antigen (HBSAg) at screening. 29. Subjects with evidence of an active infection during the Screening period. 30. Subjects with any identified congenital or acquired immune-deficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection or immunosuppressant treatment). 31. Subjects who have gone through major surgical procedure within 60 days of randomization or have had prior organ transplantation. 32. Subjects which have received a live/attenuated vaccine within 30 days of study randomization. Note: Coronavirus 2019 (COVID-19) vaccines (including booster) and killed (inactivated) vaccines used for seasonal influenza or pneumococcal conjugate vaccines are allowed. 33. Female subjects who are pregnant or breastfeeding. 34. Subjects that have participated in an investigational trial of a drug or device either within 60 days of randomization; or where the study drug half-life is greater than 12 days, at least 5 half-lives need to have passed from the last dose of investigational drug prior to randomization. 35. Subjects with any other condition, clinically significant disorders, or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements.
Safety Assessments	The safety evaluations will include: • Adverse events, including infusion site reactions • Concomitant medication use • Vital signs (supine blood pressure [BP], heart rate [HR], respiratory rate [RR], and body temperature) • 12-Lead electrocardiogram (ECG) • Physical examination

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	- Safety laboratory tests (blood chemistry, complete blood count [CBC], liver tests, and urine analysis) - Local tolerability (evaluation of infusion site reactions) Time points for each evaluation are described in 0.
Pharmacokinetic Assessments	Blood samples (5 mL each) for determination of CM-101 serum concentrations will be collected following multiple administrations during the DB treatment period using specific enzyme-linked immunosorbent assay (ELISA) at the following time points: - Visits 1 and 5 (Treatments 1 and 5; Days 0 and 84): pre-dose within 90 minutes before dosing, at end of infusion (“Time=0”)*, and at 2 hours after the End of Infusion (EoI) (all post-infusion blood draws are within ± 10 min of the assigned time point). - Visits 2-4 (Treatments 2-4; Days 21, 42, and 63): pre-dose within 90 minutes before dosing - SF1 (Day 7): a single assessment during the visit CM-101 serum concentrations will be evaluated following multiple administrations during the OL treatment period using specific ELISA at the following time points: - Visit 6 (OL Treatment 1; Day 105): pre-dose. - Visits 8, 11, and 14 (OL Treatments 3, 6, and 9; Days 147, 210, and 273): at pre-dose within 90 minutes before dosing, at the EoI (time=0)*, and at 2 hours post EoI - SF2/EOT-OL and SF3/EOS (Days 7, 336, and 420): a single assessment during the visit * Note: Since actual end of infusion may be somewhat longer or shorter than the exact planned 60 minutes, time=0 (EoI) will be the actual end of IP infusion (prior to saline IV line wash). A total of 24 PK samples will collected over 420 days. The following PK parameters will be calculated: - Pre-dose plasma concentration (C_0) - Observed maximum CM-101 plasma concentration (C_{max}) - Time to C_{max} (T_{max}) - Area under the curve (AUC) to the final concentration limit of quantitation (AUC_{last}) and to infinity (AUC_{∞}) - Terminal elimination rate constant (λ_z) - Terminal elimination half-life ($t_{1/2}$) An exposure-response assessment will be made comparing endpoints (such as change in ALP level relative to baseline) and serum biomarkers to the average exposure of CM-101 (e.g., AUC or concentration at steady state [C_{ss}]) to help define an optimal dose of CM-101 for this subject population.
Interim Analyses	Up to 3 interim analyses (IAs) are planned during the conduct of the study. The first IA will be conducted when approximately 14 subjects have completed their Week 15 visit. These IAs will evaluate all safety and tolerability data, as well as PK data. A subset of the PD markers in the study will be analyzed at this time. These prespecified PD

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	measures will be evaluated at baseline, and as a change from baseline at Week 15. Safety data will be assessed to enable the initiation of dosing in the 20 mg/kg dose level cohort. Pharmacokinetic data will be analyzed to confirm exposure; interpatient variability and effect sizes on the study outcome measures will be analyzed in order to inform study dose level cohort sample sizes. The safety, PK, and PD data listings provided to the DMC will not contain subject identification numbers or any other unblinding treatment information; however, the DMC may ask to unblind an individual subject and/or group data, as appropriate. The Sponsor or any designee (except for the Sponsor's unblinded personnel), subjects, Investigator(s), and trial site staff will remain blinded to treatment allocations during the interim data analysis and will not participate in the DMC closed session discussion. Trial recruitment will continue during the interim data collection and analysis. A second unblinded IA will occur when all subjects complete the double-blind portion of the study through Week 15. The IA will evaluate all available safety, tolerability, PK, and PD and efficacy data from all cohorts in the study. Dosing in the open-label portion of the study will continue during the IA data collection and analysis. A separate Statistical Analysis Plan (SAP) will be generated for the IA data, describing the conduct of the IA in detail.
Statistical Methods	<u>Analysis Sets</u> The analysis sets are the following: • Intent-to-Treat (ITT) Analysis Set: The ITT analysis set includes all subjects randomized into the study. • Modified Intent-to-Treat (mITT) Analysis Set: The mITT analysis set includes all randomized subjects who have received at least one dose of CM-101 or placebo. • Fifteen-week (15W) Analysis Set: The 15W analysis set includes all randomized subjects who have completed at least a 15-week treatment period (i.e., completed Treatment 5; Study Day 84) and have no major protocol deviations. • Per Protocol (PP) Analysis Set: The PP analysis set includes all randomized subjects who have completed the 15-week treatment and initial safety follow-up periods (i.e., completed EOT-DB; Study Day 105) and have no major protocol deviations. • PK Analysis Set: The PK analysis set includes all randomized subjects who have received CM-101/placebo treatment and have provided sufficient blood samples for PK evaluation, without relevant deviations interfering with the PK evaluations.

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	<u>Efficacy Analysis</u> Secondary efficacy analyses of change from baseline through to Week 15 in serum ALP, ELF scores, hepatic biochemistry, and hepatic function parameters will use a Two-Sample t Test for mean difference for comparisons of each CM-101 dose cohort with placebo. In addition, secondary efficacy analyses of ALP response rates, defined as reduction of ALP to $1.3 \times \text{ULN}$, or a combination of ALP reduction to $1.5\text{--}1.3 \times \text{ULN}$ with an at least 40% reduction from baseline, will compare CM-101 treatment group vs placebo at Week 15 using a Cochran-Mantel-Haenszel test. Each CM-101 dose cohort will be compared with placebo in this binary outcome as well. <u>Safety Analysis</u> This study has multiple safety-related endpoints, including the frequency and severity of treatment-emergent AEs (TEAEs), changes in vital signs, changes in clinical safety laboratories, and evaluation of infusion site reactions. Analysis of safety and tolerability endpoints will be compared by CM-101 treatment group and placebo. The incidence of TEAEs and treatment-emergent SAEs will be tabulated by System Organ Class and Preferred Term for each treatment group, and similarly by severity and relationship to treatment. Laboratory parameters and vital signs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The change from Baseline will also be summarized. Electrocardiograms will be summarized by treatment group using frequency at each visit. The shift from baseline will also be summarized. Full details of the statistical methodology, analyses, and outputs will be detailed in the SAP. All statistical analyses will be carried out using SAS® Version 9.3 or higher under Windows® 2008 Terminal.
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LIST OF ABBREVIATIONS

Acronym	Definition
15W	Fifteen-week Analysis Set
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (also known as glutamate-pyruvate transaminase-SGPT)
ANCOVA	analysis of covariance
ANIT	Alpha-naphthylisothiocyanate
AST	Aspartate aminotransferase (also known as glutamate-oxaloacetate transaminase-SGOT)
AUC	Area under the curve
AUC ₍₀₋₇₂₎	AUC from 0 to 72 hours
AUC _∞	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC _{last}	Area under the plasma concentration-time curve from time of administration up to the last time point
AUC _t	Area under the concentration-time curve from time 0 up to time 't'
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C4	7 α -hydroxy-4-cholesten-3-one
Ca 19-9	Cancer antigen 19-9
CBC	Complete blood count
CCL24	Chemokine (C-C motif) ligand 24
CCR3	C chemokine receptor type 3
CDAI	Crohn's Disease Activity Index
CDC	Complement-dependent cytotoxicity
CDR	Complementarity-determining region
CHO	Chinese hamster ovary
C _{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CRO	Clinical Research Organization

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Acronym	Definition
Css	Concentration at steady state
CTCAE	Common Terminology Grades for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CX3CR1	C-X3-C motif chemokine receptor 1
DB	Double-blind
DILI	Drug induced liver injury
DMC	Data Monitoring Committee
EC50	Half maximum effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELF	Enhanced liver fibrosis
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoI	End of Infusion
EOS	End of study
EOT	End of Treatment
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GRAS	Generally recognized as safe
HA	Hyaluronic acid
HBSAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV Ab	Hepatitis C virus antibody
HDL	High-density lipoprotein
HGB	Hemoglobin
HIV	Human immunodeficiency virus

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Acronym	Definition
HR	Heart rate
hr, hrs	Hour, hours
hsCRP	High-sensitivity C-reactive protein
IA	Interim analysis
IBD	Inflammatory Bowel Disease
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN γ	Interferon gamma
IgG	Immunoglobulin G
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
iRT	Interactive response technology
ISR	Infusion site reactions
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
Kg	Kilogram
kPa	kilopascal
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
mAb	Monoclonal antibody
MAD	Multiple ascending dose
MCP1	Monocyte chemoattractant protein 1
MDR2	Multidrug resistance 2
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model of end stage liver disease
mg	Milligram
mITT	Modified Intent-to-Treat

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Acronym	Definition
mL	Milliliter
MRI	Magnetic resonance imaging
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
OCA	Obeticholic Acid
OL	Open-label
PAN-CK	Pan-cytokeratin
PD	Pharmacodynamic
PIIINP	Amino-terminal pro-peptide of type III procollagen
PIS	Subject Information Sheet
PK	Pharmacokinetics
PP	Per protocol Analysis set
PRO-C3	Pro-peptide of type III collagen
PRO-C5	Pro-peptide of type V collagen
PSC	Primary Sclerosing Cholangitis
PT	Preferred Term
Q3W	Once every three weeks
RA	Regulatory authority
RANTES	Regulated on activation, normal T cell expressed and secreted
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous, -ly
SF	Safety Visit
SOA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
t _{1/2}	Elimination half-life
TAA	Thioacetamide

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Acronym	Definition
TEAE	Treatment emergent adverse event
TIMP-1	Tissue inhibitor of metalloproteinases 1
TK	Toxicokinetic
Tmax	Time to maximum concentration
TNF	Tumor necrosis factor
TNF- α	Tumor necrosis factor-alpha
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
WHO	World Health Organization
α -SMA	Alpha smooth muscle actin
β -hCG	Beta human chorionic gonadotrophin

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1. INTRODUCTION

1.1. Background

Cholestasis is a common symptom of liver injury and is characterized as the interruption of bile flow from hepatocytes to the intestine, which leads to bile acid accumulation in the liver, resulting in oxidative stress, inflammation, apoptosis, and fibrosis. Cholestasis is highly associated with a wide spectrum of liver diseases, including acute hepatitis, primary sclerosing cholangitis (PSC) (Lindor, 2009; Lazaridis, 2016) and primary biliary cholangitis (EASL, 2009; Tabibian, 2015). There are very few effective therapies for cholestasis, with ursodeoxycholic acid (UDCA) being the only approved drug by the Food and Drug Administration (EASL, 2009; Sclair, 2015; Tabibian, 2015). Primary sclerosing cholangitis is a disease of the bile ducts that causes inflammation and obliterative fibrosis of bile ducts inside and/or outside of the liver. The biliary epithelium shows an activated phenotype in PSC, including an expansion of the peribiliary gland system. Although the details are not clear, this activation is likely important for peribiliary fibrosis development and subsequent cirrhosis, through interactions with hepatic stellate cells, portal myofibroblasts, or both. This pathological process impedes the flow of bile to the intestines and can lead to cirrhosis of the liver, liver failure, and other complications, including bile duct and liver cancer. The underlying cause of the inflammation remains unknown, but elements of autoimmunity and microbial dysbiosis have been described (Charatcharoenwitthaya, 2006) and are suggested by the observation that approximately 75% of individuals with PSC also have inflammatory bowel disease (IBD), most often ulcerative colitis (Chapman, 2010). Liver transplantation is the definitive treatment for PSC, though only those individuals with PSC who develop advanced liver disease will ultimately require a transplant (Sclair, 2015). Etiology and pathogenesis of PSC pose many unresolved questions and remain a scientific and clinical challenge. Primary sclerosing cholangitis is idiopathic (i.e., at present there is no known cause). While thought to be an autoimmune disease, PSC does not demonstrate a clear response to immunosuppressants. Thus, many experts believe it to be a complex, multifactorial (including immune-mediated) disorder and perhaps one that encompasses several different hepatobiliary diseases (O'Hara, 2013; Tabibian, 2015). Although the pathophysiology underlying this disease has not yet been fully elucidated, animal models of PSC have provided contributions in dissecting the molecular basis of this disease, focusing on the role of cytokines and chemokines as important pathogenetic mediators of liver inflammation and fibrosis (Agostini, 2006; Landi, 2014). Chemokines are a group of small chemotactic proteins that induce the migration of various kinds of cells that are thought to be involved in the etiology of PSC. Elevations of Eotaxin-3 and Eotaxin-1 in PSC and Eotaxin-3 in primary biliary cirrhosis and autoimmune hepatitis suggest an Eotaxins-C chemokine receptor type 3 (CCR3)/C-X3-C motif chemokine receptor 1 (CX3CR1) axis model for the pathophysiology of the liver damage and fibrosis associated with these diseases (Landi, 2014). Chemokine (C-C motif) ligand 24 (CCL24, Eotaxin-2) is a chemokine that promotes cell trafficking and regulates inflammatory and fibrotic activities through the CCR3 complex. The chemokine is expressed in activated T cells, monocytes, activated fibroblasts, endothelial cells, and hepatocytes. The chemokines induce chemotaxis and activation of CCR3 expressing cells: eosinophils (Kitaura, 1996; Ponath, 1996; Jepsen, 2015), T-cells (Bocchino, 2002), fibroblasts (Bhattacharyya, 2011), hepatocytes, and

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hepatic stellate cells (Jin, 2017). Chemomab is developing CM-101, a humanized immunoglobulin(Ig)G1 anti-human CCL24 monoclonal antibody for treatment of fibrotic and inflammatory diseases, specifically PSC and Non-alcoholic fatty liver disease.

1.2. CM-101

1.2.1. Description

CM-101 is a humanized IgG1 monoclonal antibody against human CCL24 derived from a murine hybridoma using Composite Human Antibody™ technology (antibody humanization technology).

[REDACTED]

[REDACTED]

[REDACTED] Release testing and stability studies will be conducted in accordance with International Council for Harmonisation (ICH) guidelines

CM-101 targets the soluble chemokine CCL24. CCL24 is a chemokine that promotes cell trafficking and regulates inflammatory and fibrotic activities through the CCR3 complex, especially by inducing chemotaxis of monocytes (Jose, 1994; Kitaura, 1996; Ponath, 1996), T-cells (Bocchino, 2002), and fibroblasts (Bhattacharyya, 2011). CCL24 is produced by several inflammatory cells and its receptor CCR3 is present on eosinophils, T-cells, monocytes, and fibroblasts.

CM-101 drug product will be provided as a preservative free, aseptically filled solution for intravenous (IV) infusion formulated

[REDACTED]

1.2.2. Nonclinical Studies

1.2.2.1. Proof of Concept Studies In-Vitro and In-Vivo

In vitro and in vivo studies have been conducted to evaluate the activation of CCR3 expressing cells in the presence of CCL24 and CM-101. The activation potency of chemokines was measured through calcium release into the cytosol. In vitro data has demonstrated that CM-101 causes a significant reduction in CCR3 expressing cells activation with

[REDACTED] These data suggest that CM-101 may attenuate activation of CCR3 expressing cells, including inflammatory and fibrotic cells expressing CCR3 involved in the development of PSC, nonalcoholic steatohepatitis (NASH), systemic sclerosis

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and other fibrotic conditions. Furthermore, results [REDACTED]

1.2.2.2. CM-101 Effect on PSC

The pathological process of PSC is multifactorial and is influenced by both environmental and genetic factors. Although the pathological mechanism is complex and incompletely understood, it appears to involve autoimmune, inflammation, and fibrosis processes.

Chemomab evaluated the levels of CCL24 in the sera of subjects with PSC, collected under ethics approval. CCL24 was found to be highly and differentially expressed in cholangiocytes and immune cells in the liver of subjects with PSC compared to healthy livers. Hepatic stellate cells, characterized as the main effector cells in liver fibrosis, due to their capacity to transdifferentiate into collagen-producing myofibroblasts (Bhattacharyya, 2011). The transition to myofibroblast is correlated with the expression of alpha smooth muscle actin (α -SMA). Chemomab activated human hepatic stellate cells with CCL24. Cells treated with recombinant CCL24 or with sera containing high CCL24 levels demonstrated a more robust transition to myofibroblasts, measured by α -SMA expression. This transition was significantly attenuated when CM-101 (10 μ g/mL) was co-incubated with the sera, prior to cells' stimulation.

CM-101 and its murine surrogate [REDACTED] were evaluated in-vivo using several experimental PSC animal models. The experimental PSC models include the alpha-naphthylisothiocyanate (ANIT) diet in mice, the bile duct ligation model in rats and the MDR2 knockout model in mice.

The ANIT diet model is frequently used as an experimental tool to identify mechanisms of liver injury caused by bile duct damage due to the bile duct hyperplasia, biliary fibrosis and liver toxicity that develop following ANIT treatment. [REDACTED] was administered in a treatment mode from Week 2 (once the disease was established), twice weekly, in doses of 2.5 mg/kg and 5 mg/kg. [REDACTED] significantly attenuated liver enzymes and histological liver assessment in the ANIT induced PSC model.

In the bile duct ligation experimental liver fibrosis model in Sprague Dawley rats, 10 mg/kg of CM-101 was administered IV twice weekly for 2 weeks treatment and showed a significant antifibrotic effect, reflected by significantly reduced levels of Sirius red staining by 50% when compared to bile duct ligated rats treated with vehicle. In addition, proliferation of cholangiocytes assessed by pan-cytokeratin (PAN-CK) positive cell staining was significantly reduced following CM-101 treatment.

The antifibrotic, anti-inflammatory and anti-cholestatic effects of [REDACTED] were further tested in the MDR2 knock out mouse model. The multidrug resistance 2 (MDR2) knockout mice spontaneously progress to severe biliary fibrosis and cirrhosis therefore this model highly correlates with the human disease. [REDACTED], at the 5 mg/kg dose level, administered twice weekly IP from Week 6, was able to reduce alkaline phosphatase (ALP), bile acid and liver fibrosis.

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The direct anti-fibrotic effect of CM-101 was demonstrated using the thioacetamide (TAA)-induced liver fibrosis model in rats and mice. In the TAA rat model, CM-101 was administered at 2.5 mg/kg IV twice weekly, in a treatment mode, during Weeks 4 through 8. Significant reduction of 82% in fibrotic areas (measured by Sirius red staining) was demonstrated that was further supported by reduction of liver collagen qualified by Sircol™ (Biocolor, United Kingdom). In the mice TAA model, [REDACTED] was administered at 2.5 mg/kg or 10 mg/kg subcutaneously (SC) twice weekly. After 12 weeks of TAA exposure, all vehicle-treated animals had developed liver fibrosis (measured by Sirius red staining) and treatment with both 10 and 2.5 mg/kg [REDACTED] reduced fibrosis by 50%. Inflammation decreased from a score of 2.8 in the TAA group to 1.8 in both 10 and 2.5 mg/kg [REDACTED] treated groups.

For detailed description of the pre-clinical models, please refer to the Investigator's Brochure.

1.2.2.3. Preclinical Safety Evaluations

Preclinical safety evaluations included ex-vivo safety evaluations, in vivo safety toxicology studies and pharmacokinetic (PK) evaluations.

1.2.2.4. Ex-Vivo Evaluation

Ex vivo safety evaluation for antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and proinflammatory cytokine secretion was performed. CM-101 showed no effect on these parameters in blood samples taken from healthy donors (n=10) compared to control IgG treatment.

For detailed description of the ex-vivo experiments, please refer to the Investigator's Brochure.

1.2.2.5. GLP Safety Toxicology Studies

In vivo Good Laboratory Practice (GLP) safety toxicology studies were conducted in mice and cynomolgus monkeys.

A 4-week repeat-dose GLP toxicology study was performed in C57bl mice to evaluate the toxicity and toxicokinetic profile of CM-101-D8. CM-101 (D8) is the parental hybridoma derived antibody containing the same complementarity-determining regions (CDRs) as the humanized CM-101 antibody. CM-101 (D8) was administered via IV injection once every week for a total of 5 doses at doses of 10 mg/kg, 50 mg/kg, and 100 mg/kg, which reflects a 10-fold increase of the planned human dose for the suggested Phase 2a study (10 mg/kg).

No obvious treatment related adverse reactions, no gross or microscopic pathological findings, and no cases of treatment related mortality were observed. In addition, all blood and urine tests were found to be within normal ranges for mice. Evaluation of pro-inflammatory cytokines secretion following administration was evaluated at 1, 4, 8, and 24 hours post administration. No significant elevation was seen in interleukin (IL)1b, IL2, IL4, IL5, IL10, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFNγ), and tumor necrosis factor-alpha (TNF-α) compared with the control animals. Taken together, the GLP repeat-dose toxicology study in mice showed no treatment-related toxicities at any dose level, and the no observed adverse effect level was determined to be 100 mg/kg.

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Toxicokinetic evaluation showed that [REDACTED] exhibited a linear correlation between the administered dose and the serum levels. The terminal half-life remained quite constant at all three doses and similar between the genders (a [REDACTED]). The accumulation factor during repeated treatments (calculated as the area under the curve [AUC] ratio for each dose between five treatments and one treatment) were within the expected accumulation factor in such PK profiles. All samples were negative for antibodies to [REDACTED]. Anti-drug antibodies (ADA) levels were below detection point at all time points and at all dose levels.

To support long term clinical administration with this CM-101, the long-term GLP toxicology program was performed using SC administration. Subcutaneous administration is not intended for subjects with PSC at this stage; however, SC administration may be used later in development and for other target indications for CM-101 (i.e., NASH). Considering the acceptable levels of serum exposure achieved by using the SC route this study supports the IV administration.

A 6-month GLP repeat-dose toxicology study in cynomolgus monkeys to support long-term clinical administration with CM-101 representative of the clinical material was conducted. CM-101 was administered via SC administration once every 2 weeks for a total of 26 weeks, followed by an 8-week recovery period, at doses of 5 mg/kg, 25 mg/kg, and 50 mg/kg. Repeated SC administration of up to 50 mg/kg showed no obvious treatment-related adverse reactions, no clinical signs or injection site reactions, and no cases of treatment-related mortality were observed. In addition, all blood and urine tests were found to be within normal ranges for monkeys. There were no treatment-related organ weight changes and no treatment-related necropsy findings. There were no treatment-related histopathology findings. The toxicokinetics (TK) of CM-101 in cynomolgus monkey serum following every two weeks subcutaneous administration of CM-101 for 26 weeks was evaluated. Following administration the time to maximum concentration (T_{max}) for CM-101 was observed between 8 and 72 hours. Systemic exposure (maximum plasma concentration [C_{max}] and AUC from 0 to 72 hours [$AUC_{(0-72)}$]) increased with increasing dose on Days 1 and 169 (Week 26). The increase in systemic exposure (C_{max} and $AUC_{(0-72)}$) was relatively dose proportional from 5 to 50 mg/kg/adm on Days 1 and 169. Following repeated dosing, systemic exposure on Day 169 (for main animals) and Day 183 (for recovery animals) was generally slightly higher compared to Day 1. No consistent sex difference in exposure was observed. Three samples from treated animals (2 from the CM-101 high dose group and 1 animal from the placebo group) were confirmed ADA positive, however there was no obvious correlation between positive ADA results and CM-101 serum concentrations or systemic exposure.

For detailed description of GLP Toxicology study, please refer to the Investigator's Brochure.

1.2.3. Clinical Studies

In humans, CM-101 has been tested in two Phase 1a single ascending dose studies using both IV and SC administration in healthy volunteers, and in a Phase 1b multiple administration study in subjects with non-alcoholic fatty liver disease with normal liver function. CM-101 is currently being evaluated in a multiple dose study in subjects with NASH.

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The completed human studies include:

- Phase 1 single IV administration, escalating dose, study in healthy volunteers (Protocol no.CM-101-I-001)
 - Tested doses 0.75-10 mg/kg compared with placebo: n=32
- Phase 1 single SC administration study in healthy volunteers (Protocol no.CM-101-SC-001)
 - Tested dose 5 mg/kg compared with placebo: n=8
- Phase 1b, repeated dose (5 administrations; once every three weeks [Q3W]) safety study in male and female subjects with non-alcoholic fatty liver disease with normal liver function tests (Protocol no. CM-101-I-002; The SPARK study) (Tested two dose levels: 2.5 mg/kg IV compared to placebo and 5 mg/kg SC compared to placebo; n=8 in each cohort)

In human studies CM-101 was found to be safe and well tolerated at all tested doses. No severe or serious drug-related adverse events (AEs) occurred during any of the studies and no subjects discontinued their participation prematurely due to drug related AEs (one subject in the Phase 1b study experienced a non-drug related serious adverse event (SAE); diagnosis of meningioma and had to discontinue after 4 of the planned 5 treatments). All IV drug administrations were completed as planned and no events were recorded following the SC injections. CM-101-related AEs were mild in intensity and resolved without sequelae. Evaluation of various serum cytokines in the Phase 1a single IV study revealed no clinically meaningful changes for any of the tested cytokines at any time point following CM-101 dosing.

The PK profile of CM-101 was typical of monoclonal antibodies (mAbs) that undergo neonatal Fc receptor (FcRn)-mediated recycling with a terminal half-life [REDACTED] when given IV and [REDACTED] when given as SC injection supporting administration of CM-101 at a frequency of once every 2 to 4 weeks.

Pharmacodynamic (PD) assessment was conducted by evaluating the levels of target engagement. Analysis of total CCL24 (CM-101-bound and unbound) levels revealed, across studies, a significant and dose dependent engagement of CM-101 to its target, evident by increase of total CCL24 which reflects its sequestration from the intravascular space and generation of CM-101-CCL24 bound complexes.

1.3. Rationale

1.3.1. Study Rationale

Primary sclerosing cholangitis is a rare, chronic cholestatic liver disease characterized by progressive inflammation, fibrosis, and destruction of the intrahepatic and extra-hepatic bile ducts with no identifiable cause (Eaton, 2013; Hirschfield, 2013). Primary sclerosing cholangitis disease progression can vary, but typically begins in portal tracts; fibrosis and commensurate inflammatory responses induce a progressive spread of the fibrotic condition. The unmet medical

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need for PSC is very high. Drugs that have anti-inflammatory, anti-fibrotic effects, or can improve bile acid flow may have beneficial effects in PSC.

Chemomab is developing CM-101, a humanized IgG1 anti-human CCL24 monoclonal antibody for treatment of fibrotic and inflammatory diseases, including in adult subjects with PSC and NASH.

Nonclinical data have demonstrated that CM-101 binds and targets CCL24 and attenuates process mediated by CCL24 and its receptor CCR3 in various in-vitro, ex-vivo and in-vivo models. CM-101 shows high affinity and selectivity to human CCL24, which is produced by several inflammatory cells and its receptor CCR3 is present on immune cells, fibroblasts, and endothelial cells. In vitro functional data demonstrate that CM-101 is a potent inhibitor of CCL24 induced mechanisms. CM-101 results in a significant inhibition of migration and activation of immune cells, and fibroblasts, including hepatic stellate cells.

CM-101 and its murine surrogate [REDACTED] were evaluated in-vivo using several experimental PSC animal models. The experimental PSC models include the ANIT diet in mice, the bile duct ligation model in rats and the MDR2 knockout model in mice.

The ANIT diet model is frequently used as an experimental tool to identify mechanisms of liver injury caused by bile duct damage due to the bile duct hyperplasia, biliary fibrosis and liver toxicity that develop following ANIT treatment. [REDACTED] was administered in a treatment mode from Week 2 (once the disease was established), twice weekly, in doses of 2.5 mg/kg and 5 mg/kg. [REDACTED] significantly attenuated liver enzymes and histological liver assessment in the ANIT induced PSC model.

In the bile duct ligation experimental liver fibrosis model in Sprague Dawley rats, 10 mg/kg of CM-101 was administered IV twice weekly for 2 weeks treatment and showed a significant antifibrotic effect, reflected by significantly reduced levels of Sirius red staining by 50% when compared to bile duct ligated rats treated with vehicle. In addition, proliferation of cholangiocytes assessed by PAN-CK positive cell staining was significantly reduced following CM-101 treatment.

The antifibrotic, anti-inflammatory, and anti-cholestatic effects of [REDACTED] were further tested in the MDR2 knock out mouse model. The MDR2 knock out mice spontaneously progress to severe biliary fibrosis and cirrhosis therefore this model highly correlates with the human disease. [REDACTED] at the 5 mg/kg dose level, administered twice-weekly investigational product (IP) from Week 6, was able to reduce ALP, bile acid, and liver fibrosis.

The direct anti-fibrotic effect of CM-101 was demonstrated using the TAA induced liver fibrosis model in rats and mice. In the TAA rat model, CM-101 was administered at 2.5 mg/kg IV twice weekly, in a treatment mode, during Weeks 4-8. Significant reduction of 82% in fibrotic areas (measured by Sirius red staining) was demonstrated that was further supported by reduction of liver collagen qualified by Sircol. In the mice TAA model, [REDACTED] was administered at 2.5 mg/kg or 10 mg/kg SC twice weekly. After 12 weeks of TAA exposure, all vehicle-treated animals had developed liver fibrosis (measured by Sirius red staining) and treatment with both 10 and 2.5 mg/kg [REDACTED] reduced fibrosis by 50%. Inflammation decreased from a score of 2.8 in the TAA group to 1.8 in both 10 and 2.5 mg/kg [REDACTED] treated groups.

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The suggested Phase 2a, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of 10 and 20 mg/kg CM-101 given Q3W in subjects with PSC.

1.3.2. Rationale for Dose Selection

This is a Phase 2a, double-blind, placebo-controlled study in male and female adult subjects with PSC (Protocol no. CM-101-PSC-101; The SPRING study), with an open-label treatment extension. In this study, the safety, tolerability, PK, and activity of CM-101 in PSC will be evaluated. CM-101 activity will be measured using changes in ALP levels, enhanced liver fibrosis (ELF) score, biochemical response (liver enzyme levels and lipid profile), as well as a panel of biomarkers of fibrogenesis, liver fibrosis, and inflammation. The study will be conducted using IV administration of CM-101 given Q3W for a period of 48 weeks.

The planned doses for the study are 10 and 20 mg/kg. These dose levels were selected to frame the expected efficacious exposure range of CM-101 (based on animal pharmacology studies and target expression in subjects) and to explore the relationship between dose, exposure, and biological and clinical response in subjects with PSC. The goal is to identify the optimal CM-101 dose to advance to larger efficacy studies in this patient population.

The dose range selected for this first in patients with PSC dose-finding study is based on a combination of nonclinical efficacy and safety data, and the safety data observed in CM-101 clinical trials performed to date.

1.3.2.1. Human Safety Data

The safety, tolerability, and PK of the single ascending dose (SAD) IV administration of 0.75-10 mg/kg and the multiple ascending dose (MAD) IV administration of 2.5 mg/kg and SC 5 mg/kg of CM-101 has been evaluated in three completed studies: two Phase 1a studies (CM-101-I-001, CM-101-SC-001) and a Phase 1b study in subjects with non-alcoholic fatty liver disease (CM-101-I-002). The average C_{max} seen in the single 10 mg/kg IV administration was [REDACTED]. Multiple PK simulations using combinations of the available PK data from these studies were performed to assess the expected exposures following the Q3W IV administration of 20 mg/kg of CM-101. The expected average (steady state) CM-101 concentrations ranged between [REDACTED] 0 µg/mL, and the predicted C_{max} values ranged between [REDACTED] 0 µg/mL.

1.3.2.2. Nonclinical Safety Data

CM-101 was evaluated in a series of nonclinical toxicology studies. The results of a pivotal GLP repeat-dose toxicology study demonstrated a no observed adverse event level of 100 mg/kg in mice and 50 mg/kg in cynomolgus monkeys, which were the highest tested doses. Regarding CM-101 exposures at the no observed adverse event levels, the C_{max} values observed were [REDACTED] µg/mL in mice, and [REDACTED] µg/mL in monkeys, with an average serum concentration of [REDACTED] at steady state. The maximum exposures (C_{max}) observed in these safety studies are [REDACTED] (monkey) and [REDACTED] (mice) higher than those observed in the Phase 1 clinical study (CM-101-I-001), and [REDACTED] (monkey) and [REDACTED] (mice) higher than the exposures anticipated following Q3W IV administration of 20 mg/kg.

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Finally, the steady state concentration seen in monkeys was [REDACTED]-fold higher than the anticipated steady state following Q3W IV administration of 20 mg/kg CM-101.

1.3.2.3. Nonclinical Efficacy Data

CM-101 was tested in four PSC relevant mice models: an MDR2 knockout model, a chronic ANIT-induced cholestasis model, a bile duct ligation model, and a TAA (thioacetamide)-induced liver fibrosis model. In all models, efficacy was observed with steady state CM-101 serum exposures of between [REDACTED] µg/mL, which is in the range of anticipated exposures in humans following IV administration of 5-10 mg/kg Q3W. Based on the preclinical efficacy experimental model data and incorporating the higher expression levels of CM-101's target, the cytokine CCL24, observed in the livers of subjects with PSC, the dose range for IV administration that is anticipated to be efficacious in humans is 5-20 mg/kg.

Taken together, CM-101 doses of 5-20 mg/kg by IV administration are anticipated to be safe and well tolerated, and to provide an exposure range sufficient to assess the biological and clinical activity of CM-101 in subjects with PSC. Finally, to further ensure the safety of the planned dosing of 20 mg/kg IV, enrollment in this highest dose cohort will not begin until a review of all available safety and tolerability data from both an on-going Phase 2 trial in NASH (CM-101-NASH-201), and an interim analysis of the 10 mg/kg dosing cohort in this PSC trial is conducted, and a recommendation to initiate enrollment has been provided by the Data Monitoring Committee (DMC).

For detailed description of the CM-101 clinical studies, please refer to the Investigator's Brochure.

1.3.3. Rationale for Population Selection

1.3.3.1. Concomitant Autoimmune Diseases

The population selected for this Phase 2a study includes subjects with PSC that may have concomitant stable IBD and possible overlap syndrome with autoimmune hepatitis as long as the Investigator does not consider the autoimmune hepatitis as the predominant cause for the liver injury. The typical patient with PSC is a 30 to 40-year-old male. Approximately 75% of patients with PSC also have IBD, most often suffer from ulcerative colitis, and up to 25% of patients may also have other autoimmune diseases (Saarinen, 2000).

CM-101 was tested using several models of non-liver autoimmune and inflammatory diseases such as rheumatoid arthritis, interstitial pulmonary fibrosis, and systemic sclerosis. In all models, reduction in inflammatory status was observed in addition to the overall reduction in disease state. When tested in multiple liver disease models, CM-101 demonstrated an anti-inflammatory effect in addition to its antifibrotic activity. In the Phase 1 study in healthy volunteers a panel of serum cytokine levels were measured at pre-dose, and 1, 8, and 24 hours post-CM-101 administration (the following cytokines were measured: IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, IFN γ and TNF- α). No clinically meaningful changes were noted for any of the tested cytokines at any time point following CM-101 dosing. Furthermore, no correlation between the tested doses or treatment (CM-101 or placebo) and cytokine levels were evident.

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Overall, CM-101 treatment in subjects suffering from PSC with concomitant stable IBD or overlap syndrome with autoimmune hepatitis might result in additional beneficial effect to the concomitant disease with no demonstrated evidence of excess risk for disease worsening.

1.3.3.2. Serum Creatinine Levels

Serum creatinine is influenced by gender, age, the amount of muscle mass, and physical activity. The expected subject population that will be recruited are 30–40-year-old males that are in relatively good condition (outside of their PSC), a large portion of which will be active and will participate in physical activity.

Antibodies are eliminated by either excretion or catabolism. Unlike small molecules, mAbs are too large to be filtered by the kidneys and are not eliminated in the urine. Thus, elimination occurs mostly through intracellular catabolism by lysosomal degradation to amino acids after uptake by either pinocytosis, an unspecific fluid phase endocytosis, or by a receptor-mediated endocytosis process (Ryman, 2017).

CM-101 is a humanized IgG1 monoclonal antibody. In pre-clinical safety testing and in the phase 1 SAD study in healthy volunteers no effect of CM-101 treatment on renal function was noted. We therefore defined the upper limit of acceptable serum creatinine levels for recruitment at 1.4 mg/dL.

For detailed description of the pre-clinical and clinical results, please refer to the Investigator's Brochure.

1.4. Possible Risks

CM-101 is a first-in-class antibody directed against human CCL24. In the toxicology studies (short-term mice and long-term non-human primates) and in SAD MAD studies in humans CM-101 did not demonstrate overt toxicities, therefore there are no special or focused group of possible AEs that should be specifically monitored. However, CM-101 is a new entity and special attention should be directed to any abnormalities, which might be encountered.

Possible toxicities could be related to the study drug administration (IV infusion) or to tissues that express CCL24.

- Local reactions
 - Infusion site reactions might occur as with any IV administered drugs. Pain, fever, chills, shakes, itching, rash, hyper- or hypotension might occur. Infusion-related adverse events often occur within the first 24 hours after infusion, and may be treated, if needed, with supportive treatment as indicated.
- Immune activation
 - Although not expected as it was not seen in animals or humans, any drug that attenuates the function of the immune system can cause system activation. The extreme activation cytokine storm is an adverse event that may initially look like an allergic reaction or hypersensitivity but is distinguished by more sustained and

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profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and TNF- α . Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis, and acute renal failure. A cytokine storm is not expected with CM-101 based on its mechanism of action and experience gained from animals and humans.

- Hepatotoxicity
 - Hepatotoxicity has not been observed in animals or humans however since the liver is the organ on which the activity of CM-101 is expected, careful attention to liver enzymes will be given.
- Human anti-human antibodies
 - Assays have been developed and all subjects will be tested for emergence of anti-CM-101 antibodies.
- Fatigue

The Investigator should exercise clinical judgment and thoroughly investigate, by means of additional laboratory testing, imaging or other diagnostic modalities that are not currently called for in the Schedule of Assessments (SOA) to evaluate any suspected adverse event, as well as to promptly alert the Medical Monitor.

The selected CM-101 doses for this study are 10 and 20 mg/kg given as IV infusion over 1 hour. This selected dose reflects exposure to CM-101 that are supported by the GLP toxicology studies. Overall, the safety profile obtained to date suggests that this risk is acceptable.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective of this study is to determine the safety and tolerability of multiple dose levels of the anti-human CCL24 monoclonal antibody CM-101 in adult subjects with PSC.

2.1.2. Secondary Objectives

To evaluate the activity of CM-101 as measured by a decrease in serum ALP levels and reductions in ELF scores, clinical biochemistry response to treatment (liver enzyme levels and lipid profile), CM-101 PK, PD measures, and immunogenicity (ADA).

2.1.3. Exploratory Objectives

To assess the effect of CM-101 administration to subjects with PSC on liver stiffness, and serum inflammatory and fibrotic markers, as well as other PD parameters. In addition, target engagement by measurement of serum CCL24 levels will be evaluated.

2.2. Endpoints

2.2.1. Primary Endpoint

This study has multiple safety-related endpoints including the frequency and severity of treatment-emergent AEs (TEAEs), changes in vital signs, changes in clinical safety laboratories and evaluation of infusion site reactions over the 15-week double-blind (DB) treatment period.

2.2.2. Secondary Endpoints

1. Safety-related endpoints include the frequency and severity of TEAEs, changes in vital signs, changes in clinical safety laboratories, and evaluation of infusion site reactions over the 48-week DB and open-label (OL) treatment periods.
2. Change from baseline through Week 15 in serum ALP levels by treatment cohort
3. Change from baseline through Week 15 in ELF score by treatment cohort
4. Change from baseline through Week 15 in ALP response rates, defined as reduction of ALP to $1.3 \times$ upper limit of normal (ULN), or a combination of ALP reduction to $1.5\text{--}1.3 \times$ ULN with an at least 40% reduction
5. Percent change from baseline through Week 15 in liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transferase [GGT])
6. Change from baseline through Week 15 in liver fibrosis markers as measured by pro-peptide of type III collagen (PRO-C3) and pro-peptide of type V collagen (PRO-C5)

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7. Elucidation of the serum PK profile of repeated administrations of CM-101
8. Evaluation of the development of ADAs following repeated administrations of CM-101 over a 15- and 48-week period.

2.2.3. Exploratory Endpoints

1. The effect of repeated administrations of CM-101 on the CM-101 target (CCL24) and on other relevant cytokines and chemokines.
2. Change over time in serum inflammatory markers as measured by high-sensitivity C-reactive protein (hsCRP), monocyte chemoattractant protein 1 (MCP1), IL-6, regulated on activation, normal T cell expressed and secreted (RANTES), and IL-1.
3. Change from baseline through Week 15 in liver stiffness using Transient Elastography (preferably Fibroscan™)
4. Change from baseline through Week 15 in ELF response defined as a reduction of ≥ 0.5 in ELF score
5. Change from baseline through Week 48 on serum ALP, ELF, liver enzymes, liver fibrosis markers, serum inflammatory markers, and liver elastography

Additional evaluations of cytokines and inflammatory and fibrotic markers may be conducted using blood tests collected during the study.

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3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, multiple-dose, cohort-based study evaluating the safety and efficacy of CM-101 in subjects with PSC as their predominant disease. Up to 68 subjects who provide written informed consent and meet all of the inclusion and none of the exclusion criteria will be randomized to receive either CM-101 (N=50 subjects) at doses of 10 mg/kg or 20 mg/kg (25 subjects in each CM-101 dose level) or matching placebo (N=18 subjects) in approximately 5:2 active-to-placebo ratio. Randomization of placebo subjects will be blocked to ensure that 9 placebo subjects are enrolled into each dose cohort (10 and 20 mg/kg). Study drug, defined as CM-101 or placebo, will be administered as an IV infusion given over 60 minutes (± 5 minutes). The IP is defined as CM-101.

Enrollment into each CM-101 dose level cohort will be done sequentially. Subjects will be randomized into the 10 mg/kg dose cohort (N=25) followed by the 20 mg/kg dose cohort (N=25). The initiation of the 20 mg/kg dose cohort will occur only after a review of all available safety and tolerability data from a planned interim analysis of the study is completed, and advancement to this higher dose level is recommended by the CM-101 DMC.

This study will consist of a Screening period, a DB treatment period, an OL treatment period, and a Safety Follow-up period. The timing of study visits, study assessments, and associated time windows are presented in the SOA (Appendix 1). The study design schematic is depicted in Figure 1.

Prior to any Screening Visit assessments, subjects will be consented into the study and sign the Informed Consent form (ICF). Subjects will be screened for eligibility and consented during the Screening period up to 42 days prior to study drug administration. Subjects not meeting the Inclusion/Exclusion criteria for entry in the study will not be eligible for the study and may be screened up to one additional time as detailed in Section 4.5.

During the DB treatment period, subjects will receive 5 total dose administrations of study drug (IP or placebo) Q3W for a coverage of 15 weeks. After completing the DB treatment period, subjects may elect to enroll in an OL treatment period. In the OL treatment period, subjects will receive a dose of IP Q3W for 11 administrations for a coverage of 33 weeks, resulting in a combined total coverage of 48 weeks.

Subjects who do not elect to continue treatment in the OL dosing period will undergo an End of Treatment (EOT)-DB visit at Week 15 (Day 105), a Safety Follow-up Call at Week 21 (Day 147), and an End of Study (EOS) visit at Week 27.

Eligible subjects who continue treatment in the OL treatment period will receive CM-101 at either a 10 mg/kg or 20 mg/kg dose commencing at Week 15 (OL Treatment 1), and the subjects will undergo an EOT-OL visit at Week 48 (Day 336), a Safety Follow-up Call at Week 54 (Day 378), and an EOS visit at Week 60 (Day 420).

Male and female adults, ages 18 to 75 inclusive, with PSC and a serum ALP of at least $1.5 \times$ ULN will be included in this study. Eligibility will be based on a diagnosis of large duct PSC of

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more than 24 weeks' duration based on chronic cholestatic liver biochemistry alongside consistent cholangiography, and the absence of secondary etiologies. Subjects with small duct PSC without large duct PSC will not be enrolled. Subjects must have no new clinical concern of cholangiocarcinoma within the last 12 months prior to randomization. All participating subjects will have a transabdominal ultrasound done as part of the Screening procedures. Subjects with ulcerative colitis are eligible for recruitment with a Partial Mayo score of ≤ 3 (Appendix 3) with no individual sub-score exceeding 1 point. Subjects with ulcerative colitis must have undergone colonoscopy with biopsy confirming no dysplasia or colorectal cancer within 18 months of randomization, and no history of colectomy (at any time). Subjects with Crohn's Disease must be in remission defined as a Crohn's Disease Activity Index (CDAI) < 150 (Appendix 4).

Subjects on treatment with ursodeoxycholic acid (UDCA) therapy must be treated at a stable dose not greater than 23 mg/kg per day for at least 12 weeks prior to Screening. Subjects receiving other concomitant medications need to be on stable therapy for at least 12 weeks prior to the first study treatment day (randomization).

Regardless of treatment period, all study drug administrations will be done in the clinical research facility (i.e., under observation of study staff however the study does not involve hospitalization). Subjects will remain under medical observation for 2 hours post-dosing for all administrations in both DB and OL treatment periods, unless either a reaction to the study drug administration occurs, or in the Investigator's judgment, the subject's safety warrants a longer observation post dosing during a specific visit. Subjects will be contacted by phone 3 days following each study drug administration visit (Treatments 1-5). In addition, following the first study drug administration, a safety visit will take place 7 days after the study drug administration date (Safety Visit 1; SF1).

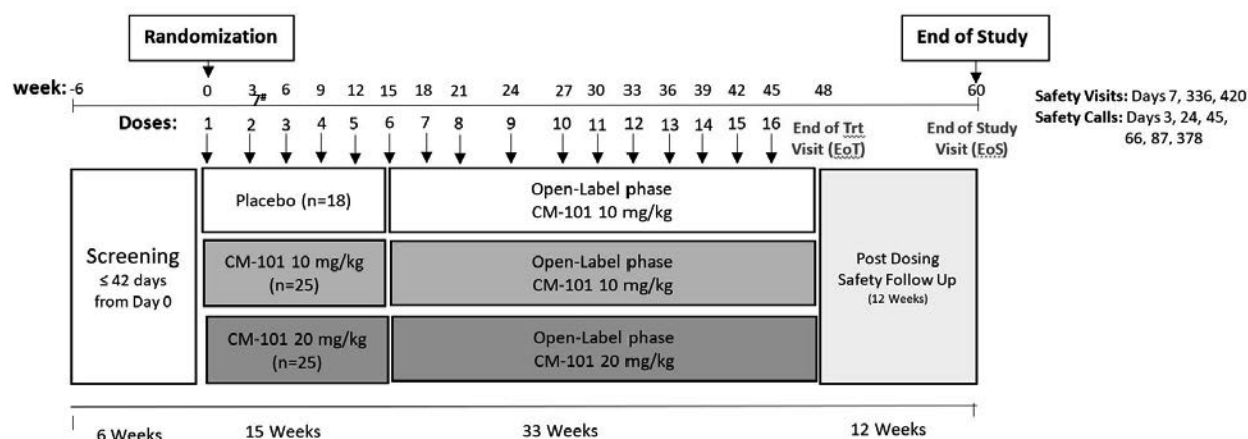
During the study, blood testing will be done for safety laboratory evaluations, liver enzyme measurements, lipid profiles, ADA, PK, and PD analyses. In addition, liver fibrosis markers (e.g., [REDACTED] serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES, and IL-1), and other relevant cytokines and chemokines will be evaluated. Changes in liver stiffness will be evaluated using Transient Elastography (preferably Fibroscan). Fatigue will be assessed at each treatment visit and at the Safety Visit 2 (SF2)/EOT visit using a Fatigue Severity Scale questionnaire. The detailed time points for study assessments are described in Section 5 and in Appendix 1.

A DMC has been assembled to review safety data collected in this trial as well as all ongoing CM-101 trials. The DMC will meet at predefined time points (at least three times a year) and on an as-needed basis based on enrollment, treatment milestones, and safety. Additional DMC details are described in Section 9.11.

Subjects will be asked to continue using their pre-study ongoing medications at stable doses for the duration of the DB portion of the study.

Subjects retain the right to withdraw from the study at any time.

Figure 1: Study Design Schematic



3.2. Number of Subjects

A total of 68 subjects, both male and female, aged between 18 and 75 years, inclusive, are planned for enrollment across 2 dose cohorts in the study.

3.3. Study Duration

Study duration for each participating subject will be up to 66 weeks (up to 33 weeks for patients not entering the Open-label Treatment Period) as follows:

- **Screening Period:** Up to 42 days (6 weeks) prior to randomization
- **Double-blind Treatment Period:** 15 weeks; CM-101 or placebo will be given as IV infusion Q3W for 5 administrations
- **Open-label Treatment Period:** 33 weeks; CM-101 will be given as IV infusion Q3W for 11 administrations
- **Follow-up Period:** 12 weeks starting at the SF2/EOT Visit (Day 336) and ending at the SF3/EOS Visit (Day 420).

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4. STUDY POPULATION

Male and female adults, ages 18 to 75 inclusive, with large duct PSC and a serum ALP of at least $\times 1.5$ ULN will be included in this study. Each subject will undergo Screening procedures within up to 42 days prior to randomization to assess eligibility to participate in the study.

4.1. Inclusion Criteria

Subjects must meet all inclusion criteria to be eligible for the study:

1. Males and females, age 18 to 75 years, inclusive.
2. Diagnosis of large duct PSC (intrahepatic and/or extrahepatic) of more than 24 weeks' duration (defined as cholestatic serum liver tests with consistent magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography showing sclerosing cholangitis once secondary causes of sclerosing cholangitis have been excluded).

Note: Subjects must have cholangiographic changes showing sclerosing cholangitis in order to be eligible for the study. Subjects will be eligible if cholangiography has been performed within 24 weeks prior to randomization but there is clinical evidence of large duct PSC for more than 24 weeks' duration.

3. No significant clinical concern for cholangiocarcinoma based on clinical, laboratory, or imaging findings in the 12 months preceding randomization.

Note: All subjects will have a transabdominal ultrasound done as part of the screening procedures.

4. Serum ALP greater than $1.5 \times$ ULN in Screening blood tests.
5. Subjects receiving UDCA must receive a stable dose for ≥ 12 weeks prior to Screening and must not exceed 23 mg/kg/day during this time.
6. Concomitant IBD is allowed, but not required, and must meet the following stability criteria:
 - a. Subjects with ulcerative colitis:
 - i. Must either be in remission or have mild disease. Remission is defined as a Partial Mayo score of ≤ 2 with no individual sub-score exceeding 1 point. Mild disease is defined as a Partial Mayo score of ≤ 3 with no individual sub-score exceeding 1 point.
 - ii. Must have undergone colonoscopy with biopsy confirming no dysplasia or colorectal cancer within 18 months of randomization, and no history of colectomy (at any time).
 - b. Subjects with Crohn's Disease must be in remission as defined by a CDAI < 150 .
 - c. If receiving concomitant medication for their IBD, dose must be stable for ≥ 12 weeks prior to screening and dose should remain stable during the DB portion of the study.

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7. Subjects receiving concomitant medications for their PSC must be on stable therapy for ≥ 12 weeks prior to randomization and plan to remain on that stable dose during the DB portion of the study.
8. Female subjects of childbearing potential (defined as sexually mature women who have not undergone surgical sterilization or who have not been naturally postmenopausal for at least 24 consecutive months for women ≤ 55 years; for women > 55 years 12 consecutive months) must have a negative serum pregnancy test prior to starting study treatment. Sexually active women of childbearing potential must agree to use a highly effective method of contraception from the Screening Visit throughout the study period including 18 weeks post last dose. See Section 8.5 for acceptable methods of contraception.
9. Male subjects, if not vasectomized, must agree to use barrier contraception (condom plus spermicide) during heterosexual intercourse from screening through to study completion and for 90 days from the last dose of study investigational medicinal product.
10. Subjects must be able to understand and provide a signed, written ICF.
11. Subjects receiving fenofibrate or other fibrates must be on a stable dose for ≥ 24 weeks prior to Screening and plan to remain on that stable dose during the DB portion of the study.

4.2. Exclusion Criteria

The clinically predominant disease must be PSC. Therefore, subjects must not meet any exclusion criteria to be eligible for the study:

1. Subjects with presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations.
2. Subjects with presence of competing etiology of liver disease (including, but not limited to, viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, IgG4-associated cholangitis, primary biliary cholangitis, etc.) are excluded from the study. Subjects with possible overlap syndrome with autoimmune hepatitis are excluded if the Investigator considers autoimmune hepatitis as the predominant liver injury.
3. Subjects with small duct PSC in the absence of large duct disease.
4. Subjects with percutaneous biliary drain or bile duct stent or subjects who had required biliary drainage within 12 weeks of Screening.
5. Subjects that have undergone prior biliary surgery (laparoscopic or open surgery) other than those who at the time of screening are more than 6 weeks after cholecystectomy without surgical complications.
6. Subjects with evidence of cirrhosis, as determined by local transient elastography (preferably Fibroscan) values of ≥ 14.4 kPa obtained during the Screening period. In case

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of a fibrosis staging discrepancy between a recent (≤ 12 months) liver biopsy staging and the transient elastography results, eligibility will be based on the liver biopsy staging.

7. History of cirrhosis and/or hepatic impairment (Child-Pugh classes A, B and C), and/or hepatic decompensation including ascites, encephalopathy, or variceal bleeding.
8. Subjects who have undergone or are planned for liver transplantation or with current model of end stage liver disease (MELD) score ≥ 16 .
9. Subjects with AST or ALT values $> 5 \times$ ULN as determined at Screening.
10. Subjects who show 'clinically significant' lab changes (as judged by the Investigator) at Screening will be excluded.
11. Subjects with serum total bilirubin values $> 3 \times$ ULN at Screening.
12. Subjects with known Gilbert's syndrome or a history of elevations in unconjugated (indirect) bilirubin $> \text{ULN}$.
13. Subjects with international normalized ratio (INR) > 1.5 which does not correct on vitamin K replacement, in the absence of anticoagulants.
14. Subjects with serum creatinine $> 1.4 \text{ mg/dL}$ ($123 \mu\text{mol/L}$) and/or a platelet count $< 100 \times 10^9/\text{L}$
15. Subjects with history of cholangiocarcinoma or a high clinical suspicion of cholangiocarcinoma, as indicated by clinical presentation, laboratory tests or imaging of a functional dominant stricture.
16. Subjects with elevated cancer antigen 19-9 (Ca 19-9) value ($> 129 \text{ U/mL}$) within 12 months prior to Screening unless Ca 19-9 levels have been stable and clinical evaluation and repeated magnetic resonance imaging (MRI) within the same time period has not provided evidence of cholangiocarcinoma.
17. Subjects with a prior biliary stricture necessitating intervention should be stable for ≥ 24 weeks prior to randomization without intervention, or episode of cholangitis, and should show a low level of clinical suspicion of cholangiocarcinoma.
18. Subjects with current known portal hypertension with complications, including known gastric or large esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds, or related therapeutic or prophylactic interventions (e.g., beta blockers, insertion of variceal bands or transjugular intrahepatic portosystemic shunt).
19. Subjects with active malignancy (diagnosed and/or treated within 3 years of randomization), other than:
 - a. adequately treated non-metastatic basal cell skin cancer;
 - b. squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to randomization;
 - c. history of cervical carcinoma in situ that has been adequately treated and that has not recurred.

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Note: subjects with history of malignancy (i.e., > 3 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the Sponsor or Medical Monitor on a case-by-case basis prior to randomization.

20. Subjects with a ‘clinically significant’ (as judged by the Investigator) unexplained weight loss during the 24 weeks prior to randomization.
21. Subjects showing deleterious effects of alcohol abuse (as assessed by the Investigator) or that consume excessive amounts of alcohol (> 14 units/week for both females and males; for the purposes of this study one unit of alcohol is considered to be equal to 8 gr).
22. Subjects with known or suspected acute cholangitis in the 90 days prior to randomization, including cholangitis treated with antibiotics within the 90 days.
23. Subjects experiencing flare in colitis activity within 90 days of randomization requiring intensification of therapy beyond baseline maintenance treatment or use of oral prednisone > 10 mg/day (or equivalent), start or dose change of biologics ≤ 12 weeks before screening and or hospitalization for colitis within 90 days of randomization.
24. [*Note EC removed in v4.0*]
25. Subjects treated with or who are expected to begin treatment with fenofibrate or other fibrates or subjects who had a change in dose within 24 weeks of Screening, or subjects who are not planned to remain on a stable dose throughout the DB portion of the study.
26. Subjects that use any prohibited medication as described in Section 8.2.
27. Subjects who have a known history of hypersensitivity reaction to CHO-derived antibodies, CM-101, or any of the formulation excipients.
28. Subjects with known chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or that have positive hepatitis B surface antigen (HBSAg) at Screening.
29. Subjects with evidence of an active infection during the Screening period.
30. Subjects with any identified congenital or acquired immune-deficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection or immunosuppressant treatment).
31. Subjects who have gone through major surgical procedure within 60 days of randomization or have had prior organ transplantation.
32. Subjects who have received a live/attenuated vaccine within 30 days of study randomization.

Note: Coronavirus 2019 (COVID-19) vaccines (including booster) and killed (inactivated) vaccines used for seasonal influenza or pneumococcal conjugate vaccines are allowed.
33. Female subjects who are pregnant or breastfeeding.

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34. Subjects that have participated in an investigational trial of a drug or device either within 60 days of randomization; or where the study drug half-life is greater than 12 days, at least 5 half-lives need to have passed from the last dose of investigational drug prior to randomization.
35. Subjects with any other conditions, clinically significant disorders, or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements.

4.3. Subject Identification

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.4. Subject Withdrawal Criteria

A subject is free to withdraw consent and/or discontinue participation in the study at any time, for any reason, without prejudice to further treatment. The Investigator must withdraw any subject from the study if a subject requests to be withdrawn. A subject may also be withdrawn from the study at any time for safety reasons based on Investigator judgment.

4.4.1. Discontinuation of Study Treatment

Study treatment may be stopped, delayed, or prematurely discontinued by the subject or the Investigator for reasons including, but not limited to:

- Request of regulatory agency, Sponsor, primary care physician, or Investigator
- Subject withdrawal of consent
- Adverse event
- Subjects that develop any of the following during the study:
 - bacterial cholangitis

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- IBD flare; where “flare” is defined as follows: ulcerative colitis flare: Partial Mayo Score ≥ 5 , and Crohn’s Disease flare: CDAI ≥ 250
- stricture requiring intervention
- drug induced liver injury (DILI)
- Subject is unwilling or unable to continue the study or is lost-to-follow-up
- Subject is non-compliant with study procedures/study protocol
- Investigator decides that withdrawal from the study is in the best interest of the subject
- Subject needs medication that is not allowed in the protocol
- Female subject becomes pregnant (see Section 4.4.1.1 for additional information)
- Any clinically significant change in subject’s medical condition
- Any delay in treatment beyond 7 days must be discussed with the Sponsor or Medical Monitor.

Please see Section 9.10 for guidelines for the assessment, monitoring, and criteria for drug interruption in potential DILI cases.

Investigators are encouraged to consult with the Sponsor’s Medical Monitor prior to a subject discontinuation from the study.

4.4.1.1. Pregnancy of a Female Subject

If a female subject becomes pregnant, the subject must stop study drug administration immediately and be withdrawn from the study. The course of all pregnancies, including perinatal and neonatal outcome, regardless of whether the subject has discontinued participation in the study, will be followed until resolution, including follow-up of the health status of the newborn to 6 weeks of age. Congenital abnormalities/birth defects in the offspring of subjects should be reported as an SAE if conception occurred during this study. Consent will be collected from the pregnant partner as per local requirements before any data is collected.

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

However, all pregnancies occurring during this study (in subjects or female partners of subjects) are to be reported in the same time frame as SAEs (24 hours) by completing the Pregnancy Notification Form and faxing or emailing it to the Sponsor and/or delegate.

4.4.2. Subject Withdrawal

The Investigator should withdraw the subject from the study if they believe that participation is no longer in the subject’s best interest, or in the event of study termination by the Sponsor. If the

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subject elects to withdraw from the study, reason(s) for withdrawal should be documented on the subject's electronic case report form (eCRF) when possible. The Investigator must notify the Sponsor and/or delegate as soon as possible if any subject is prematurely discontinued or withdraws their consent from the study.

The Investigator will discuss with the subject procedures for withdrawal and any additional care or treatment alternatives available at that time with the subject.

If a subject withdraws consent from the study, the subject should be encouraged to complete all Early Termination Visit assessments as described in Section 5.1.5. It is vital to obtain follow-up data for any subject withdrawn due to an AE or abnormal laboratory test finding. In any case, every effort must be made to undertake safety follow-up procedures.

Data collected until subject withdrawal will be retained and included in the analysis of the study in accordance with local rules and regulations. A subject who withdraws from the study may request that their study samples collected and not tested be destroyed.

4.4.3. Follow-Up After Discontinuation or Withdrawal

For a subject who is discontinued because of a related TEAE, the TEAE must be followed until the event is resolved or deemed stable. Any subject withdrawn or discontinued from the study prematurely because of an IP-related AE or termination of the study will be considered to have completed the study.

Subjects who discontinue from the study early and prior to completing all study participation should complete the Early Termination Visit assessments as described in Section 5.1.5.

4.4.4. Lost to Follow-up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

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

- Attempt to contact the subject and reschedule the missed visit(s) as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule
- Make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address) and document these efforts in the subject's medical record
- Ascertain if the subject wishes to and/or should continue in the study
- Consider the subject lost to follow-up once the aforementioned steps have been taken and contact with the subject has not been regained and document the reason for lost to follow-up, if known

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4.5. Re-Screening of Subjects

A screen failure occurs when a patient who has consented to participate in the clinical study is not subsequently randomized into the study for any reason. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Subjects who were screen failed and have not been randomized or dosed may be rescreened one time with Medical Monitor approval. [REDACTED]

[REDACTED] Depending on the timing of rescreening, repetition of some assessments may not be required based on consultation with the Medical Monitor.

4.6. Eligibility for the Open-Label Treatment Period

Subjects who have completed the DB treatment portion of the study will be eligible to participate in the OL treatment portion. The decision to continue into the open-label portion of the trial will be made by the subject and their Investigator. The subject must be willing and able to participate in the protocol mandated safety and CM-101 administration procedures. The decision to continue in the open-label portion of the study should be made prior to or during the Week 15 visit. In order to be eligible for the open-label portion, the administration of study drug during the blinded portion of the trial must have been observed to be safe and well tolerated.

Subjects who have completed Treatment 5 before the implementation of the OL treatment portion of the study will be able to join the OL treatment on a case-by-case basis at the judgment of the Medical Monitor.

4.7. Study Stopping Rules

The subject's or a site's participation in the study may be discontinued by the Sponsor at any time and for any reason. Additionally, it is agreed that, for reasonable cause, the Investigator may terminate the trial at his/her site at any time. Potential reasons may be, but are not limited to, any of the following:

- Occurrence of AEs unknown to date in respect to their nature, severity, and duration or the unexpected incidence of known AEs
- Unacceptable risk, any relevant toxicity, or a considerable negative change in the risk/benefit ratio assessment based on any data derived from this study, other clinical trials, or toxicological studies.
- Medical or ethical reasons affecting the continued performance of the study
- Poor performance or compliance of the site/subject
- The subjects may be exposed to unacceptable health risks

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- Regulatory authority request

In the event a decision is made to terminate the study prematurely, the Sponsor and/or delegate will notify the appropriate regulatory agencies and Investigators of all participating sites within 3 calendar days. The Investigators, in turn, will be responsible for notifying the Institutional Review Board (IRB)/Independent Ethics Committee (EC).

Any potential implications for participants and consequences to the results in terminating the trial early will be detailed in the “End of Study Declaration Form”.

A record of the decision to terminate the study prematurely, and all related correspondence, will be retained in the Trial Master File.

Subjects who are still enrolled at the time of study termination will undergo all procedures planned for the SF2 (EOT-DB or EOT-OL; Study Day 105 or 336), Safety Follow-up Call (Day 147 or 378), and SF3 (EOS visit; Day 189 or 420) as close as possible to 3, 9, and 15 weeks following their last treatment date, respectively.

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5. STUDY PROCEDURES AND ASSESSMENTS

Study procedures and assessments are described below. All assessments are to be performed according to the timing and frequency described in the SOA (Appendix 1). Detailed laboratory tests and assessments are provided in Appendix 2.

5.1. Description of Study Visits

5.1.1. Screening Period (Visit Screening/Study Days -42 to 0)

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study.

Documentation of the personally signed and dated informed consent of each subject, using the study-specific ICF, is required before initiating the Screening process. A complete medical history will be obtained from the subject including demographic data and any procedures performed in the past 5 years in order to assess the subject's medical condition (such as colonoscopies, biopsies, imaging reports, etc.). Screening laboratory tests may be repeated within the Screening period, prior to administration of study drug, to rule out laboratory error, if any. This will be done at the discretion of the Investigator and with prior approval of the Medical Monitor. The Screening period may be extended under special circumstances with the explicit approval of the Medical Monitor.

The following should be performed/collected at the Screening Visit after obtaining informed consent:

- Demographic information
- PSC medical history, including imaging data (such as magnetic and endoscopic retrograde cholangiopancreatography) and liver biopsy data and/or samples, if available
- Prior medications and AEs
- Physical examination (complete)
- Height, weight, and BMI (calculated as kg/m²)
- Vital signs: supine and standing blood pressure (BP), in order to rule out orthostatic hypotension, supine heart rate (HR), respiration rate (RR), and body temperature (oral or tympanic)
- 12-Lead ECG
- Safety laboratory assessments (complete blood count [CBC], biochemistry, and urinalysis)
- Blood sampling for liver enzyme measurements (ALP, ALT, AST, GGT, total bilirubin).
- Blood sampling for coagulation tests

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- Blood sampling for serology tests (HBSAg, hepatitis C virus antibody (HCV Ab), HIV)
- Blood sampling for Ca 19-9 (only for subjects with no test results within 12 months prior to Screening)
- Blood sampling for serum pregnancy test – for females of childbearing potential
- Completion of Pruritus 5-D itch scale questionnaire by the subject
- Completion of Fatigue Severity Scale questionnaire by the subject
- Transabdominal ultrasound
- Transient Elastography (preferably using Fibroscan)
- Inclusion/exclusion criteria review
- Liver tissue biopsy (collect if available stored tissue from biopsy in prior 12 months)

Once all the Screening results are obtained, eligibility to participate in the study will be assessed by the Investigator or designee.

5.1.2. Double-Blind Treatment Period

5.1.2.1. Visit 1 - Treatment 1 (Study Randomization)

Dosing day 1 will be designated as "Study Day 0".

Subjects will be admitted to the clinical research facility in the morning of the treatment dosing day after a 10-hour fast. Subjects will be interviewed by study personnel regarding concomitant medications and any change in their health/medical history status or diet since the Screening Visit. Subjects will be requested not to change their lifestyle habits with emphasis on diet, physical exercise, and the use of chronic medication (e.g., onset or cessation of special diets, such as vegan, vegetarian, low carb, etc., or intensive physical activity should be delayed until the end of the study). The following activities will take place:

Pre-Dose

The following assessments and procedures will be performed, and data collected prior to dosing:

- Inclusion/exclusion criteria will be reconfirmed
- Blood sampling for liver enzyme measurements (ALP, ALT, AST, GGT, total bilirubin) and lipid profile
- Record AEs and prior medications
- Weight and BMI calculation
- Completion of Pruritus 5-D itch scale questionnaire by the subject
- Completion of Fatigue Severity scale questionnaire by the subject

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- Completion of CDAI or Partial Mayo scoring assessment (only for subjects with IBD, if IBD status worsened)
- Complete physical examination
- Vital signs (supine; within 90 minutes before dosing)
- 12-Lead ECG (within 90 minutes before dosing)
- Venous access
- Blood and urine sampling for safety laboratory assessments (CBC, biochemistry, and urinalysis)
- Blood sampling for coagulation tests
- Blood sampling for serum bile acids and 7 α -hydroxy-4-cholesten-3-one (C4)
- Blood sampling for baseline PK (within 90 minutes before dosing)
- Blood sampling for baseline PD (within 90 minutes before dosing) will include:
 - Blood sampling for baseline serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES and IL-1)
 - Blood sampling for baseline liver fibrosis marker levels (e.g., PRO-C3 and PRO-C5)
 - Blood sampling for baseline ELF score
- Whole blood sampling for immune cell sub populations evaluation (within 90 minutes before dosing)
- Blood sampling for baseline anti-CM-101 antibodies (ADA)
- Blood sampling for baseline IgG4 and IgG1
- Urine or serum pregnancy test for females of childbearing potential (if urine test is positive or inconclusive, an additional pregnancy test will be done in Serum)

Following the collection of fasted laboratory samples, subjects may have a small snack and drink before start of study drug infusion. Subjects will not be allowed food or drink (other than water) during study drug administration and until 1 hour post end of study drug infusion (EoI). There is no limitation on drinking water.

Dosing

The IP will be administered via IV infusion over 60 minutes (± 5 minutes). Administration will be done in the supine position, and immediately following EoI, subjects will remain under direct clinical supervision at the clinical research facility for 1 hour.

Note: In case the prescription is sent to the pharmacy prior to subject weight measurement for dose calculation purposes, the weight measurement from the Screening Visit can be used instead.

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Post-dose

Subjects will remain in the clinical research facility for a total of 2 hours post-dose. The following assessments and procedures will be performed after the EoI (time=0) at the time points indicated in Section 5.2 and Section 5.3:

- Vital signs (supine) (at 2 hours post EoI $\pm$ 15 minutes and prior to discharge)
- Evaluation of infusion site reactions (ISR) will be assessed using a standard ISR evaluation scale (at 2 hours post EoI $\pm$ 20 minutes); see Table 1
- Blood sampling for safety laboratory assessments (hematology and biochemistry only) at 2 hours ($\pm$ 30 min) post EoI
- Blood sampling for PK (at EoI, 2 hours post EoI $\pm$ 10 minutes)
- Blood sampling for PD (at 2 hours post EoI $\pm$ 10 minutes)
- Record AEs
- Targeted physical examination, history and symptom directed (prior to discharge)

The IV line used for drug administration will not be used for PK and other blood draws and it is recommended to remove it once the infusion has been completed. After completing the 2-hour post-dose assessments and obtaining the physician's approval, subjects will be discharged from the clinical research facility.

5.1.2.2. Safety Phone Calls Post Drug Administration (Study Days 3, 24, 45, 66, 87; $\pm$ 1 day)

A Safety Follow-up phone Call will be conducted 3 days ($\pm$ 1 day) after each drug administration on Study Days 3, 24, 45, 66, and 87. The following activities will take place:

- Review/record AEs
- Review/record concomitant medications

5.1.2.3. Safety Visit 1 - SF1 (Study Day 7; $\pm$ 3 days)

The subjects will come to the clinical research facility for Safety Visit 1 (SF1) a week after the first study drug administration (Day 7). Subjects will be interviewed by study personnel regarding concomitant medications and any change in their health/medical history status or diet since the last visit. The following activities will take place:

- Record AEs
- Record concomitant medications
- Vital signs (supine)
- Completion of CDAI or Partial Mayo scoring assessment (only for subjects with IBD, if IBD status worsened)

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- Targeted physical examination (history and symptom directed)
- Evaluation of ISR will be assessed using a standard ISR evaluation scale; see Table 1
- Blood sampling for safety laboratory assessments (hematology and biochemistry)
- Blood sampling for liver enzyme measurements (ALP, ALT, AST, GGT, total bilirubin)
- Blood sampling for PK
- Blood sampling for PD (Blood sampling for inflammatory markers [e.g., hsCRP, MCP1, IL-6, RANTES and IL-1], liver fibrosis marker levels [e.g., PRO-C3 and PRO-C5] and ELF score as part of the PD blood testing)

5.1.2.4. Visits 2-5 - Treatments 2-5 (Study Days 21, 42, 63, 84; ± 3 days)

The subjects will be admitted to the clinical research facility in the morning of the treatment dosing day after a 10-hour fast for Visit 3 (Treatment 3) and Visit 5 (Treatment 5). Visit 2 (Treatment 2) and Visit 4 (Treatment 4) do not require fasting. Subjects will be interviewed by study personnel regarding concomitant medications and any change in their health/medical history status or diet since the last visit. The following activities will take place:

Pre-Dose

The following assessments and procedures will be performed, and data collected prior to dosing:

- Record AEs
- Record concomitant medications
- Weight and BMI calculation
- Completion of Pruritus 5-D itch scale questionnaire by the subject
- Completion of Fatigue Severity Scale questionnaire by the subject
- Completion of CDAI or Partial Mayo scoring assessment (only for subjects with IBD, if IBD status worsened)
- Targeted physical examination (symptom and history directed)
- Vital signs (supine; within 90 minutes before dosing)
- 12-Lead ECG (at Visit 3 only; Treatment 3) (within 90 minutes before dosing)
- Venous access
- Blood sampling for safety laboratory assessments (CBC, biochemistry)
- Urine or serum pregnancy test for females of childbearing potential (if urine test is positive or inconclusive, an additional pregnancy test will be done in serum)
- Blood sampling for liver enzyme measurements (ALP, ALT, AST, GGT, total bilirubin)

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- Blood sampling for lipid profile (at Visit 3 and 5 only; Treatment 3 and 5)
- Blood sampling for serum bile acids and 7 α -hydroxy-4-cholesten-3-one (C4) on Visits 3 and 5 (Treatments 3 and 5) only
- Blood sampling for IgG4 and IgG1 (at Visit 3 only; Treatment 3)
- Blood sampling for PK (within 90 minutes before dosing)
- Blood sampling for baseline PD (within 90 minutes before dosing) will include:
 - Blood sampling for serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES and IL-1)
 - Blood sampling for liver fibrosis marker levels (e.g., PRO-C3 and PRO-C5)
 - Blood sampling for ELF score
- Whole blood sampling for immune cell sub populations evaluation at Visit 3 only (Treatment 3) (within 90 minutes before dosing)
- Blood sampling for immunogenicity (anti-CM-101 antibodies; ADA) at Visit 3 only (Treatment 3)

Following the collection of fasted laboratory samples at Visit 3 (Treatment 3) and Visit 5 (Treatment 5), subjects may have a small snack and drink before start of study drug infusion. Subjects will not be allowed food or drink (other than water) during study drug administration and until 1 hour post EoI. There is no limitation on drinking water.

Dosing

The IP will be administered via IV infusion over 60 minutes (± 5 minutes). Administration will be done in the supine position. Immediately following EoI, subjects will remain under direct clinical supervision at the clinical research facility for 1 hour.

Note: In case the prescription is sent to the pharmacy prior to the subject weight measurement, for dose calculation purposes, the weight measurement from the previous visit can be used instead.

Post-dose

Subjects will remain in the clinical research facility for 2 hours post dosing for all administrations, unless either a reaction to the study drug administration occurs, or in the Investigator's judgment, the subject's safety warrants a longer post dosing observation period during a specific visit.

The following assessments and procedures will be performed after the EoI (time=0) at the time points indicated in Section 5.2 and Section 5.3:

- Vital signs (supine; at 2 hours post EoI ± 15 minutes and prior to discharge, if discharge is later than 2 hours post dosing)

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- Evaluation of ISR will be assessed using a standard ISR evaluation scale (at 2 hours post EoI); see Table 1
- Blood sampling for PD (at 2 hours post EoI $\pm$ 10 minutes)
- Record AEs
- Targeted physical examination (history and symptom directed) prior to discharge

The IV line used for drug administration will not be used for PK and other blood draws and it is recommended to remove it once the infusion has been completed. After completing the post dose observation period and obtaining the physician's approval, the subject will be discharged from the day care center.

5.1.2.5. Visit 6 - EOT-DB (Study Day 105; $\pm$ 3 days)

The subjects will return to the clinical research facility for the EOT-DB treatment period visit after a 10-hour fast.

Subjects will be interviewed by study personnel regarding concomitant medications and any change in their health/medical history status or diet since the last visit. The following activities will take place:

- Record AEs
- Record concomitant medications
- Completion of Pruritus 5-D itch scale questionnaire by the subject
- Completion of Fatigue Severity Scale questionnaire by the subject
- Completion of CDAI or Partial Mayo scoring assessment (only for subjects with IBD, if IBD status worsened)
- Weight and BMI calculation
- Vital signs (supine BP, HR, RR), and body temperature (oral or tympanic)
- 12-Lead ECG
- Complete physical examination
- Evaluation of ISR will be assessed using a standard ISR evaluation scale
- Blood and urine sampling for safety laboratory assessments (CBC, biochemistry, and urinalysis)
- Blood sampling for liver enzyme measurements (ALP, ALT, AST, GGT, total bilirubin)
- Blood sampling for coagulation tests
- Blood sampling for serum bile acids and 7 α -hydroxy-4-cholesten-3-one (C4)
- Blood sampling for PK

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- Blood sampling for PD – will include:
 - Blood sampling for serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES and IL-1)
 - Blood sampling for liver fibrosis marker levels (e.g., PRO-C3 and PRO-C5)
 - Blood sampling for ELF score
- Whole blood sampling for immune cell sub populations evaluation
- Blood sampling for IgG4 and IgG1
- Blood sampling for immunogenicity (ADA)
- Transient Elastography (preferably using Fibroscan but, in any case, it must be performed with the same device model as during the Screening Visit)
- Urine or serum pregnancy test for females of childbearing potential (if urine test is positive or inconclusive, an additional pregnancy test will be done in serum)

For subjects who choose not to participate in the OL treatment portion, this visit will serve as the SF2/EOT visit. These subjects will then complete the Safety Follow-up Call (Study Day 147) and EOS (Study Day 189) visits as described in Section 5.1.4.2 and Section 5.1.4.3, respectively.

For eligible subjects who continue into the OL treatment portion, this EOT-DB visit will be considered the OL Treatment 1 Visit, and the following activities will be performed.

Pre-Dose

The following assessments and procedures will be performed, and data collected prior to dosing:

- Obtain signed and dated informed consent
- Confirmation of OL treatment eligibility
- Evaluation of the infusion site
- Venous access

Following the collection of fasted laboratory samples, subjects may have a small snack and drink before start of study drug infusion. Subjects will not be allowed food or drink (other than water) during study drug administration and until 1 hour post EoI. There is no limitation on drinking water.

Dosing

The IP will be administered via IV infusion over 60 minutes (± 5 minutes). Administration will be done in supine position, and immediately following EoI subjects will remain under direct clinical supervision at the clinical research facility for 1 hour.

Note: In case the prescription is sent to the pharmacy prior to the subject weight measurement, for dose calculation purposes, the weight measurement from the previous visit can be used instead.

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Post-dose

Subjects will remain in the clinical research facility for 2 hours post dosing unless either the occurrence of a reaction to the IP administration or if the Investigator's judgment is that the subject's safety warrants a longer post-dosing observation period during a specific visit. The following assessments and procedures will be performed after the EoI (time=0) at time points as indicated in Section 5.2 and Section 5.3:

- Vital signs (supine) (at 2 hours post EoI $\pm$ 15 minutes)
- Evaluation of ISR will be assessed using a standard ISR evaluation scale (at 2 hours post EoI $\pm$ 20 minutes); see Table 1
- Record AEs
- Targeted physical examination (history and symptom directed) prior to discharge

After completing the 2 hours post-dose assessments and obtaining the physician's approval, the subjects will be discharged from the clinical research facility.

After completion of the EOT-DB/OL Treatment 1 Visit, subjects will continue CM-101 treatment as described in Section 5.1.3.

5.1.3. Open-Label Treatment Period

5.1.3.1. Visits 7-10 and 12-16 - OL Treatments 2-5 and 7-11 (Study Days 126, 147, 168, 189, 231, 252, 273, 294, 315; $\pm$ 3 days)

Subjects will be admitted to the clinical research facility in the morning of the treatment dosing day. These visits do not require fasting. Subjects will be interviewed by study personnel regarding concomitant medications and any change in their health/medical history status or diet since the last visit. The following activities will take place:

Pre-Dose

The following assessments and procedures will be performed, and data collected prior to dosing:

- Record AEs
- Record concomitant medications
- Weight and BMI calculation
- Targeted physical examination (history and symptom directed)
- Vital signs (supine; within 90 minutes before dosing)
- Evaluation of the infusion site
- Venous access
- Blood sampling for safety laboratory assessments (CBC, biochemistry)

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- Urine or serum pregnancy test for females of childbearing potential (if urine test is positive or inconclusive, an additional pregnancy test will be done in serum)
- Blood sampling for liver enzyme measurements (ALP, ALT, AST, GGT, total bilirubin)
- Blood sampling for PK (at Visits 8 and 14; OL Treatments 3 and 9) (within 90 minutes before dosing)
- Blood sampling for PD (at Visits 8 and 14; OL Treatments 3 and 9) (within 90 minutes before dosing) will include:
 - Blood sampling for serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES and IL-1)
 - Blood sampling for liver fibrosis marker levels (e.g., PRO-C3 and PRO-C5)
 - Blood sampling for ELF score
- Liver tissue biopsy (optional collection at Visit 15 [OL Treatment 10] if historic tissue was available for subject at Screening for comparison)

Subjects will not be allowed food or drink (other than water) during IP administration and until 1 hour post EoI. There is no limitation on drinking water.

Dosing

The IP will be administered via IV infusion over 60 minutes (± 5 minutes). Administration will be done in supine position, and immediately following EoI subjects will remain under direct clinical supervision at the clinical research facility for 1 hour.

Note: In case the prescription is sent to the pharmacy prior to the subject weight measurement, for dose calculation purposes, the weight measurement from the previous visit can be used instead.

Post-dose

Subjects will remain in the clinical research facility for 2 hours post dosing unless either the occurrence of a reaction to the IP administration or if the Investigator's judgment is that the subject's safety warrants a longer post-dosing observation period during a specific visit.

The following assessments and procedures will be performed after the EoI (time=0) at time points as indicated in Section 5.2 and Section 5.3:

- Vital signs (supine; at 2 hours post EoI ± 15 minutes)
- Evaluation of ISR will be assessed using a standard ISR evaluation scale (at 2 hours post EoI); see Table 1
- Blood sampling for PK (at EoI and 2 hours post EoI ± 10 minutes) (at Visits 8 and 14; OL Treatments 3 and 9)

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- Blood sampling for PD (at EoI and 2 hours post EoI $\pm$ 10 minutes) (at Visits 8 and 14; OL Treatments 3 and 9)
- Record AEs
- Targeted physical examination (history and symptom directed) prior to discharge

The IV line used for drug administration will not be used for PK and other blood draws and it is recommended to remove it once the infusion has been completed. After completing the post dose observation period and obtaining the physician's approval, the subject will be discharged from the day care center.

5.1.3.2. Visit 11 - OL Treatment 6 (Study Day 210; $\pm$ 3 days)

Subjects will be admitted to the clinical research facility in the morning of the treatment dosing day after a 10-hour fast. Subjects will be interviewed by study personnel regarding concomitant medications and any change in their health/medical history status or diet since the last visit. The following activities will take place.

Pre-Dose

The following assessments and procedures will be performed, and data collected prior to dosing:

- Record AEs
- Record concomitant medications
- Weight and BMI calculation
- Completion of Pruritus 5-D itch scale questionnaire by the subject
- Complete physical examination
- Vital signs (supine; within 90 minutes before dosing)
- 12-Lead ECG (within 90 minutes before dosing)
- Venous access
- Blood sampling for safety laboratory assessments (CBC, biochemistry)
- Blood sampling for coagulation tests
- Blood sampling for serum bile acids and 7 α -hydroxy-4-cholesten-3-one (C4)
- Blood sampling for liver enzyme measurements (ALP, ALT, AST, GGT, total bilirubin)
- Blood sampling for lipid profile
- Blood sampling for PK (within 90 minutes before dosing)
- Blood sampling for baseline PD (at Visits 8 and 14; OL Treatments 3 and 9) (within 90 minutes before dosing) – will include:

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- Blood sampling for serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES and IL-1)
- Blood sampling for liver fibrosis marker levels (e.g., PRO-C3 and PRO-C5)
- Blood sampling for ELF score
- Whole Blood sampling for immune cell sub populations evaluation (within 90 minutes before dosing)
- Blood sampling for baseline anti-CM-101 antibodies (ADA)
- Blood sampling for baseline IgG4 and IgG1
- Urine or serum pregnancy test for females of childbearing potential (if urine test is positive or inconclusive, an additional pregnancy test will be done in serum)

Subjects will not be allowed food or drink (other than water) during drug administration and until 1 hour post EoI. There is no limitation on drinking water.

Dosing

The IP will be administered via IV infusion over 60 minutes (± 5 minutes). Administration will be done in supine position, and immediately following EoI subjects will remain under direct clinical supervision at the clinical research facility for 1 hour.

Note: In case the prescription is sent to the pharmacy prior to the subject weight measurement, for dose calculation purposes, the weight measurement from the previous visit can be used instead.

Post-dose

Subjects will remain in the clinical research facility for 2 hours post dose. The following assessments and procedures will be performed after the EoI (time=0) at time points as indicated in Section 5.2 and Section 5.3:

- Vital signs (supine) (at 2 hours post EoI ± 15 minutes)
- Evaluation of ISR will be assessed using a standard ISR evaluation scale (at 2 hours post EoI ± 20 minutes); see Table 1
- Blood sampling for PK (at EoI and 2 hours post EoI ± 10 minutes)
- Blood sampling for PD (2 hours post EoI ± 10 minutes)
- Record AEs
- Targeted physical examination (history and symptom directed) prior to discharge

The IV line used for drug administration will not be used for PK and other blood draws and it is recommended to remove it once the infusion has been completed. After completing the post dose assessments and obtaining the physician's approval, the subjects will be discharged from the clinical research facility.

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5.1.3.3. Visit 17 - EOT-OL (Study Day 336; ± 3 days)

The subjects will return to the clinical research facility for the EOT-OL visit after a 10-hour fast. For subjects who opted into the OL treatment period, this visit will serve as SF2. In addition, this visit should be performed for all subjects that discontinued their study participation prior to Week 48.

Subjects will be interviewed by study personnel regarding concomitant medications and any change in their health/medical history status or diet since the last visit. The following activities will take place:

- Record AEs
- Record concomitant medications
- Completion of Pruritus 5-D itch scale questionnaire by the subject
- Completion of Fatigue Severity Scale questionnaire by the subject
- Weight and BMI calculation
- Vital signs (supine BP, HR, RR), and body temperature (oral or tympanic)
- 12-Lead ECG
- Complete physical examination
- Evaluation of ISR will be assessed using a standard ISR evaluation scale
- Blood and urine sampling for safety laboratory assessments (CBC, biochemistry, and urinalysis)
- Blood sampling for liver enzyme measurements (ALP, ALT, AST, GGT, total bilirubin)
- Blood sampling for lipid profile
- Blood sampling for coagulation tests
- Blood sampling for serum bile acids and 7 α -hydroxy-4-cholesten-3-one (C4)
- Blood sampling for PK
- Blood sampling for PD – will include:
 - Blood sampling for serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES and IL-1)
 - Blood sampling for liver fibrosis marker levels (e.g., PRO-C3 and PRO-C5)
 - Blood sampling for ELF score
- Whole blood sampling for immune cell sub populations evaluation
- Blood sampling for IgG4 and IgG1

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- Blood sampling for immunogenicity (ADA)
- Transient Elastography (preferably using Fibroscan but, in any case, it must be performed with the same device model as during the Screening visit)
- Urine or serum pregnancy test for females of childbearing potential (if urine test is positive or inconclusive, an additional pregnancy test will be done in serum)

5.1.4. Safety Follow-up Period

5.1.4.1. Safety Visit 2 - SF2 (EOT-DB or EOT-OL Visit; Study Day 105 or 336; ± 3 days)

The SF2 will be conducted 3 weeks after completion of treatment in either the DB treatment portion or the OL treatment portion. Assessments performed at the SF2 visit will be those listed in the respective EOT-DB or EOT-OL visit.

For subjects who choose not to participate in the OL treatment period, the EOT-DB visit (Section 5.1.2.5) will serve as the SF2 Visit.

For subjects who continued into the OL treatment period, the EOT-OL visit (Section 5.1.3.3) will serve as the SF2 Visit.

5.1.4.2. Safety Follow-Up Call (Study Day 147 or 378; ± 3 days)

After completion of either the DB or OL treatment period, a Safety Follow-up Call will be conducted 6 weeks after the SF2 (EOT-DB or EOT-OL) Visit (Study Day 147 or 378; ± 3 days). The following activity will take place:

- Record AEs

5.1.4.3. Safety Visit 3/EOS Visit (Study Day 189 or 420; ± 7 days)

Subjects will return to the clinical research facility for the SF3/EOS Visit (Study Day 189 or 420; ± 7 days). The SF3/EOS Visit will take place 12 weeks after the EOT Visit.

The following activities will take place:

- Record AEs and concomitant medications
- Vital signs (supine BP, HR, RR), and body temperature (oral or tympanic)
- Targeted physical examination (history and symptom directed)
- Blood sampling for PD
- Blood sampling for PK
- Blood sampling for immunogenicity (ADA)

5.1.5. Early Termination Visits

Subjects who discontinue study treatment prematurely for the reasons specified in Section 4.4.1 should complete the Safety Follow-up Period Visits (Visits 17, 18, and 19) and perform all

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assessments as described for the SF2/EOT Visit at Week 48 (Day 336), the Safety Follow-up Call at Week 54 (Day 378), and the SF3/EOS Visit at Week 60 (Day 420). The SF2/EOT Visit will be conducted as close to 3 weeks following their last treatment date. Efforts should be made to perform the SF3/EOS as close to 15 weeks following their last treatment date. Additional procedures and evaluations will be completed as deemed necessary by the Investigator.

5.1.6. Unscheduled Visit(s) and Extenuating Circumstances

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded. Adverse event monitoring and concomitant medication recording will be performed by the Investigator during the visit. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not limited to) laboratory tests, ECG, vital signs, and a physical examination.

In the extreme case in which the subject is not able to come to a study site visit due to his/her medical condition, or the COVID-19 pandemic, or any other extenuating circumstances, study Safety Visits 1 and 3 and Study Visits 2-5 may be performed at the subject's home or a pre-designated off-site location, in accordance with local regulatory guidelines (and IRB/IEC instructions, if applicable) and with subject's consent. In the same context, visits might be shortened or diverted to phone call or video visits, in whole or in part, with the intention to record safety information and collect the maximal amount of data, as predefined by Sponsor.

5.2. Safety Assessments

Safety evaluations will be based on changes from baseline of clinical AEs (including infusion site reactions) reported by the subject or observed by the Investigator, concomitant medication use, vital signs, ECG, physical examinations, and laboratory assessments including hematology, blood chemistry, coagulation tests, and general urinalysis.

5.2.1. Adverse Events

Adverse events will be collected starting from ICF signing up until the SF3/EOS Visit (Study Day 189 or 420). From ICF signing until the first study drug administration (Day 0), only SAEs and protocol-related AEs will be reported.

From first study drug administration up until SF3/EOS Visit (Study Day 189 or 420), all AEs will be reported. These AEs will be recorded as TEAEs.

Any new AE that occurs between scheduled visits should be brought to the attention of the Investigator and recorded in the subject's medical file and on the appropriate eCRF page. During study visits, AEs should be collected after completion of the Pruritus itch scale and the Fatigue Severity Scale questionnaires by the subject.

Any AEs or clinically significant out of range laboratory results related to study drug administration should be followed up until resolution.

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5.2.2. Concomitant Medication Use

Relevant information about all concomitant drugs (including prescribed, over-the-counter, or herbal preparations) taken prior to (i.e., within 30 days of Screening) and during the trial must be recorded in the source documents and eCRF. For further details regarding concomitant medication restrictions, please see Section 8.1.

5.2.3. Vital Signs

Vital sign measurements will be recorded in supine position at all study visits (Screening, Treatment, and Safety visits). Vital signs will include BP, HR, RR, and body temperature (oral or tympanic), after the subject has rested quietly for at least 5 minutes. During Screening, standing BP will also be measured to rule out orthostatic hypotension.

Vital sign measurements will be recorded at the following time points:

- Screening visit
- All Dosing Days (Visits 1-16): prior to dosing (within 90 minutes before dosing), 2 hours post dosing ($\pm$ 15 min) and prior to discharge (if discharge is later than 2 hours post dosing).
- During Safety Visits 1, 2, and 3 (SF1, SF2, and SF3/EOS) and/or at the end of treatment (EOT, if done prior to Week 15 or Week 48).

Changes in vital signs determined by the Investigator to be clinically significant will be noted as an AE on the appropriate eCRF page(s). Such abnormalities will be closely monitored until stabilized or resolved.

5.2.4. Physical Examination and Patient Self-Report Questionnaires

Physical examination will be performed at all study site visits (Screening, Visits 1-16, and Safety Visits) before the dose is received and prior to the subject's discharge (2 hours post dose) by the Investigator or appropriate designee.

Complete physical examinations will be performed at Screening, Visits 1, 6, 11, 17 (SF2/EOT), and 19 (EOS). All others will be targeted physical examinations (history and symptom directed). Clinically significant abnormalities that are observed before administration of the first dose of IP should be reported as part of the subject's medical history. Completion of the Pruritus 5-D itch scale and the Fatigue Severity Scale questionnaires should be completed by the subject prior to any other procedure. Clinically significant changes from baseline examination at Screening or clinically significant abnormalities that are observed after first dose administration during the general physical examination will be recorded as AEs in the eCRF.

Complete physical examination should include, at a minimum, general appearance, height (Screening visit only), weight, skin, head, eyes, ears, nose, and throat, neck, lymph nodes, chest/respiratory system, cardiovascular system, abdominal region, extremities, musculoskeletal system, and mental status and neurological system.

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5.2.5. Electrocardiogram

Electrocardiogram output will be evaluated by the Investigator or appropriate designee, and the printout should be kept (signed and dated) in the source documentation file. The final decision whether the ECG findings are of clinical significance to the subject is the Investigator's responsibility.

ECG 12-Lead will be performed at the following time points:

- Screening visit/re-screening visit
- Baseline: prior to first dosing (Visit 1, within 90 minutes before dosing)
- Visit 3 (Treatment 3): prior to dosing (within 90 minutes before dosing)
- Visit 6 (OL Treatment 1): prior to dosing Visit 11 (OL Treatment 6): prior to dosing (within 90 minutes before dosing)
- SF2/EOT visit: during the visit

Any ECG abnormality determined by the Investigator to be clinically significant will be noted on the appropriate eCRF page(s) and will be considered as an AE. Such abnormalities will be closely monitored until stabilized or resolved.

5.2.6. Local Reaction at the Infusion Site

The extent of local reaction at the infusion site will be graded according to Table 1, modified from the FDA Guidance for the Industry: Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials and recorded in the appropriate eCRF page(s).

Table 1: Grading of Local Reaction

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5 – 5 cm and no interference with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Abbreviation: ER = emergency room.

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Local site reactions will be assessed at each dosing visit (V1-V16) at 2 hours $\pm$ 20 minutes after dosing and during Safety visits 1 and 2 (SF1 and SF2/EOT) and/or at SF3/EOS if done prior to Week 15 or Week 48.

5.2.7. Safety Laboratory Assessments

Safety laboratory evaluations will be performed by the site's clinical laboratories. The laboratory assessment variables are detailed in Appendix 2.

Safety blood laboratory tests will be performed at all study site visits (Screening, V1-V17, SF1, and SF2/EOT).

Urinalysis will be done at Screening, Visit 1 (pre-dose) on first dosing day, Visit 6, and at the SF2/EOT visit.

All clinically significant laboratory tests or laboratory tests of unknown significance which are outside the normal range will be repeated as clinically indicated until the values return to normal, or until the etiology has been determined and the condition is considered stable. Abnormal laboratory test results that are considered to be clinically significant by the Investigator will be reported as an AE in the eCRF.

5.2.8. Pregnancy Test

Pregnancy testing is required for females of childbearing potential and is not required for post-menopausal or surgically sterilized women. See Section 8.5 for definitions of childbearing potential and post-menopausal. At Screening, a serum beta human chorionic gonadotropin (β -hCG) pregnancy test will be done. Blood or urine tests will be done on subsequent visits and if urine test is positive or inconclusive, an additional serum β -hCG test will be performed.

5.3. Pharmacokinetic, Pharmacodynamic, Inflammatory, and Fibrosis Markers, and Immunogenicity Assessments

5.3.1. Pharmacokinetic Assessments

Blood samples (5 mL each) for determination of CM-101 serum concentrations will be collected and evaluated following multiple administrations during the DB treatment period using specific enzyme-linked immunosorbent assay (ELISA) at the following time points:

- Visits 1 and 5 (Treatments 1 and 5; Days 0 and 84): pre-dose within 90 minutes before dosing, at EoI (Time=0)*, and at 2 hours after the EoI (all post-infusion blood draws are within $\pm$ 10 minutes of the assigned time point).
- Visits 2-4 (Treatments 2-4; Days 21, 42, and 63): pre-dose within 90 minutes before dosing
- SF1 (Day 7): a single assessment during the visit

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CM-101 serum concentrations will be evaluated following multiple administrations during the OL treatment period using specific ELISA at the following time points:

- Visit 6 (OL Treatment 1; Day 105): pre-dose.
- Visits 8, 11, and 14 (OL Treatments 3, 6, and 9; Days 147, 210, and 273): at pre-dose within 90 minutes before dosing, at the EoI (time=0)*, and at 2 hours post EoI
- SF2/EOT-OL and SF3/EOS (Days 7, 336, and 420): a single assessment during the visit

***Note:** Since actual EoI may be somewhat longer or shorter than the exact planned 60 minutes, time=0 (EoI) will be the actual end of IP infusion (prior to saline IV line wash).

A total of 24 PK samples will collected over 420 days.

The following PK parameters will be calculated based on the plasma concentrations measured and the PK analysis set:

- C_0 : Pre-dose plasma concentration
- C_{max} : Observed maximum plasma concentration
- T_{max} : Time to reach the observed maximum plasma concentration
- AUC_{last} : Area under the plasma concentration-time curve from time of administration up to the last time point with a measurable concentration post dosing, calculated by linear up-logarithmic down trapezoidal summation.
- AUC_{∞} : Area under the plasma concentration-time curve extrapolated to infinity, calculated as: $AUC_{\infty} = AUC_{last} + C_{last}/\lambda_z$, where AUC_{last} is the last measurable concentration.
- λ_z : Elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve
- $t_{1/2}$: Terminal elimination half-life, defined as $0.693/\lambda_z$

The actual sample collection date and exact clock time will be entered on the PK blood collection summary page of the source data and copied to the eCRF. Sampling problems will be noted in the source documents and eCRF.

Blood may be drawn either by direct venipuncture or through an indwelling IV cannula (a different cannula than the one used for drug administration). Whenever the latter is performed, the cannula will be flushed with 1.5 mL normal saline after each sampling. In addition, 1 mL blood will be discarded before the next sample (as long as the cannula is in place) to avoid sample dilution.

The PK samples for each subject will be packaged and shipped to the analytical laboratory selected by the Sponsor.

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The blood samples labeling, handling, separation (by centrifugation) processing, freezing, and shipping will be done according to the Laboratory Manual provided by the Sponsor and/or delegate.

5.3.2. Pharmacodynamic, Fibrosis, and Inflammatory Marker Assessments

Blood samples used to determine PD and inflammatory marker parameters will be taken at the following time points:

- Visits 1 and 5 (Treatments 1 and 5; Study Days 0 and 84): 20 mL will be drawn at pre-dose (within 90 minutes before dosing), and 5 mL will be drawn at 2 hours $\pm$ 10 minutes after the EoI (Time=0)
- SF1 and SF2/EOT-OL (Study Days 7 and 336): 5 mL will be drawn at SF1, and 20 mL will be drawn at SF2/EOT-OL
- SF3/EOS (Day 420): a single assessment during the visit

OL Treatment Period

- Visits 8, 11, and 14 (OL Treatments 3, 6, and 9; Days 147, 210, and 273): at pre-dose within 90 minutes before dosing, and at 2 hours post EoI
- SF2/EOT-OL and SF3/EOS (Days 336 and 420): a single assessment during the visit

Blood samples (whole blood) to determine immune cell subpopulations (in selected countries/sites) will be taken at the following time points:

- Visit 1 (Treatment 1; Study Day 0) pre-dose (within 90 minutes before dosing)
- Visit 3 (Treatment 3; Study Day 42) pre-dose (within 90 minutes before dosing)
- Visit 6 (Study Day 105; EOT-DB, OL Treatment 1) pre-dose
- Visit 11 (Study Day 210; OL Treatment 6) pre-dose (within 90 minutes before dosing)
- SF2/EOT (Study Day 336) during the visit blood samples of 5 mL will be drawn

Pharmacodynamic parameters include target engagement, inflammatory markers, hepatic disease and fibrosis markers, and immune cell sub populations. The following will be assessed:

- Serum CCL24 levels
- Inflammatory marker levels of cytokines and interleukins (e.g., hsCRP, MCP1, IL-6, IL-1, and RANTES)
- Markers of liver disease and fibrosis, [REDACTED]
- Single cell ribonucleic acid sequencing from whole blood samples

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- IgG4 and IgG1 levels will be evaluated pre-dose at Baseline (Visit 1, Treatment 1), Visit 3 (Treatment 3; Study Day 42), Visit 6 (EOT-DB; Study Day 105; OL Treatment 1) pre-dose, Visit 11 (OL Treatment 6; Study Day 210) pre-dose (within 90 minutes before dosing), and SF2/EOT-OL (Study Day 336) during the visit.

Additional interleukins, cytokines, chemokines, fibrotic markers, and relevant PD parameters may also be tested on an exploratory research basis. The Sponsor will store and maintain all serum samples for exploratory/future research under appropriate conditions.

The blood samples labeling, handling, separation (by centrifugation) processing, freezing, and shipments will be done according to the Laboratory Manual provided by the Sponsor and/or delegate.

5.3.3. Immunogenicity

Immunogenicity as expressed by formation of ADA will be assessed at the following time points:

- Visit 1 (Treatment 1; Study Day 0) on the first dosing day pre-dose (within 90 minutes before dosing)
- Visit 3 (Treatment 3; Study Day 42) pre-dose (within 90 minutes before dosing)
- Visit 6 (EOT-DB; Study Day 105) pre-dose (OL Treatment 1 subjects only)
- Visit 11 (OL Treatment 6; Study Day 210) pre-dose (within 90 minutes before dosing)
- Visit 11 (SF2/EOT-OL; Study Day 336) during the visit
- Visit 19 (SF3/EOS; Study Day 420) during the visit.

A total of 6, 5-mL blood samples (30 mL total) will be collected. Processing of blood samples will be detailed in the Laboratory Manual provided by the Sponsor and/or delegate.

5.3.4. Liver Biopsy

If a subject has undergone a liver biopsy within 12 months prior to randomization, the tissue from that biopsy may be made available to the Sponsor. Subjects with liver biopsy tissue available at Screening will be eligible to undergo a biopsy at Visit 15 (OL Treatment 10; Study Day 294).

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6. INVESTIGATIONAL PRODUCT

6.1. Identity of Investigational Product

CM-101 is a monoclonal antibody supplied in a single-use, 20-mL vial. [REDACTED]

Matching placebo will be supplied as single use, 20-mL vials. The placebo solution contains: [REDACTED]

The composition of the active drug and placebo excipients is detailed in the Investigator's Brochure and Pharmacy Manual provided by the Sponsor and/or delegate.

6.2. Manufacturing

Chemomab is the provider of the study drug supply and matching placebo. The active ingredient is manufactured by [REDACTED] and the fill and finish of the final drug product is done at [REDACTED]. All manufacturing activities are performed under full compliance with current Good Manufacturing Practice.

6.3. Packaging and Labeling

The study drug and matching placebo will be packaged and labeled according to current Good Manufacturing Practice guidelines for drugs used in clinical trials and local relevant regulations. Details of the packaging and labeling of clinical supplies are found in the Pharmacy Manual provided by the Sponsor and/or delegate.

6.4. Shipment and Storage

All study drugs will be supplied to the sites by the Sponsor or its designee, as detailed in the Pharmacy Manual.

All study supplies should arrive at the site Pharmacy in sufficient time to enable dispensing and dosing as scheduled. The Sponsor and/or delegate will notify the site Principal Investigator (or appropriate designee) prior to dispatch of drug/placebo supplies, of the anticipated date of their arrival. Each shipment of study drug/placebo supplies for the study will be accompanied by a shipment form describing the contents of the shipment and appropriate documentation which will make it possible to retrace their composition, pharmaceutical profiles, retest dates and a confirming declaration regarding impurities and degradation products. The shipment form will assist in maintaining current and accurate inventory records. The pharmacist, or designee, will confirm the receipt of clinical supply according to the instructions provided in the shipment form, and will maintain signed drug accountability logs to be verified by the study monitor.

The investigational study drug or matching placebo will be packed and shipped to the study sites at 2-8°C in appropriate boxes with temperature loggers. If, upon arrival at the pharmacy, study drug supplies appear to be damaged or if there has been a temperature excursion, product should be quarantined at the appropriate storage conditions and not dispensed for administration, and the Sponsor and/or delegate should be contacted immediately for further instructions.

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Study drug supplies must be kept refrigerated at a controlled temperature between 2°C to 8°C (as per manufacturer labeling), in an appropriate, secure locked area with access to the study drug limited to designated study personnel.

6.5. Return of the Investigational Product

At the conclusion of the study, a final accountability of the IP will be performed by the Investigator (or designee) and verified by the study monitor. Any discrepancies identified will be indicated, with an explanation of the discrepancy. The Investigator (or designee) must return all used and unused medication or discard it, according to site regulations, in accordance with the Sponsor's and/or delegate instructions. A copy of the clinical supplies return or destruction documentation will be forwarded to the Sponsor (or designee). Drug/placebo accountability records, clinical drug/placebo supply receipts, and returns must be maintained by the Investigator (or designee). Used IV bags and needles will be discarded after use on site, according to site regulations.

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7. STUDY TREATMENTS

7.1. Allocation to Treatment

7.1.1. Double-Blind Treatment

Eligible subjects will be randomized in approximately 5:2 active-to-placebo ratio to receive CM-101 at either 10 or 20 mg/kg (n=50; 25 in each dose cohort) or placebo (n=18). Randomization of placebo subjects will be blocked to ensure that 9 placebo subjects are enrolled into each dose cohort (10 and 20 mg/kg).

7.1.2. Open-Label Treatment

Eligible subjects from the first cohort (CM-101 10 mg/kg vs placebo) will be assigned to receive CM-101 at a dose of 10 mg/kg during the open-label treatment phase.

Eligible subjects from the second cohort (CM-101 20 mg/kg vs placebo) will be assigned to receive CM-101 at a dose of 20 mg/kg during the open-label treatment phase.

7.2. Randomization Criteria

Enrollment to each CM-101 dose cohort will be done sequentially: 10 mg/kg dose cohort followed by the 20 mg/kg dose cohort.

At Study Day 0 prior to Treatment 1 and after confirmation of study eligibility, subjects will be allocated to either treatment group or placebo in approximately 5:2 active-to-placebo ratio based on a predefined randomization code (generated by the Sponsor or designee) using an Interactive Web Response System (IWRS), an iRT. The IWRS will serve as an investigational product inventory and management system and may be integrated with the trial database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to randomize and allocate the subject to the treatment. A randomization number will be assigned and IP dispensing information (i.e., vial numbers and volume to be extracted from them) will be provided while maintaining the trial blind.

No stratification will be done following protocol amendment version 3.0.

7.3. Blinding

This study includes a double-blind treatment period, during which neither the Sponsor, the subjects, the Investigators, the study staff, or any personnel involved in the subject assessments and/or monitoring will know the treatment assignments. When required, DMC members will be unblinded.

The IP/placebo dose will be prepared according to instructions provided in the study Pharmacy Manual. On each dosing day, the study drug/placebo vials will be appropriately marked by the study staff, indicating dosing date and randomization number.

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The analytical laboratory, PD laboratory, and drug supply personnel may be unblinded. Select Sponsor personnel will be unblinded for the duration of the trial.

In the absence of a medical emergency, the blinded randomization for this trial will not be revealed until all data is entered into the database, edit checks are performed, queries are closed, eCRFs are signed by the Investigator, and the database is officially locked.

7.4. Breaking the Blind

Treatment assignment will be made available to the Investigator for emergency use only through the IWRS. When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (i.e., in situations where knowledge of the blinded treatment is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as accidental unblinding or intentional unblinding following an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

Access to treatment assignments will be made available through the IWRS only to named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities, as appropriate.

7.5. Study Drug Preparation

Only suitably qualified personnel designated by or under the supervision of the site Pharmacist are authorized to prepare and dispense the IP.

Care must be taken to ensure sterility of the prepared solution, since the product does not contain any anti-microbial preservatives or bacteriostatic agents. No incompatibilities between CM-101 or the placebo and polyolefin infusion bags have been observed.

Recommended safety measures for preparation and handling of CM-101 or placebo include laboratory coats and gloves. After the IP has been prepared for administration, the total storage time of the prepared solution (combination of refrigeration and room temperature) should not exceed 8 hours, and the IP should preferably be administered within 4 hours.

Each drug administration for the 10 mg/kg dose [REDACTED] L, and the 20 mg/kg dose will be a [REDACTED], which will contain the appropriate volume of IP with a supplementation of 0.9% sodium chloride. Matching placebo will be diluted to a total volume of [REDACTED] in sterile normal saline (0.9% sodium chloride). Please refer to the Pharmacy Manual provided by the Sponsor for more details.

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7.6. Administration of the Study Drug

Study drug (CM-101 or placebo) will be administered as an IV infusion over 60 minutes (± 5 minutes), preferably with a 0.2-micron in-line filter. It is not to be administered as an IV push or bolus injection. Please refer to the Pharmacy Manual provided by the Sponsor for more details.

The time of infusion start and time of infusion end will be recorded in the source data and eCRF.

The IV line used for drug administration will not be used for PK or other blood draws and it is recommended to be removed once the infusion has been completed.

7.7. Treatment Adherence

CM-101 or placebo will be administered by the appropriately designated study staff at the investigational site, under supervision of an Investigator. The date and time that each subject is dosed will be recorded in the subject's eCRF and medical records.

7.8. Accountability and Compliance of Investigational Product

Drug accountability records must be maintained by the clinical investigation sites at all times. Shipment requests, records of study drug receipts, dispensing records, and inventory forms located at the site will be reviewed and reconciled by the study monitor periodically during and at the end of the study. For more information on how to handle remaining used and unused vials, please refer to the Pharmacy Manual provided by the Sponsor.

The subject number, dosing date, batch number, vial number(s), and quantity of study drug injected to the subject will be checked for correctness and recorded on the appropriate accountability forms. Please refer to the Pharmacy Manual provided by the Sponsor for more information.

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8. STUDY RESTRICTIONS

8.1. Prior and Concomitant Medications

Non-study medications will be classified as prior and concomitant. Prior medications are defined as those taken at least once during the 30 days before Screening and until the first treatment. Concomitant medications are defined as those taken at least once from first treatment through to the EOT-OL visit (SF2; Study Day 336). Prior medications and concomitant medications will be listed appropriately in the eCRF.

Information about the concomitant medications and treatments will be collected at each Visit. All concomitant medications given to the subject during the study will be recorded on the appropriate eCRF page.

Subjects should refrain from the use of any new prescription medications/products or change in the dose or frequency of existing therapies for treatment of their PSC or associated disease within 28 days prior to randomization (Visit 1) and until EOT-DB. The Medical Monitor should be informed of any change or addition of medication during this time period.

8.1.1. Ursodeoxycholic Acid

Subjects taking UDCA at randomization (stable dose for ≥ 12 weeks that do not exceed 23 mg/kg/day) should maintain this dose and the timing of administration of UDCA for the duration of the DB treatment part of the study (15 weeks, until EOT). Subjects who are not taking UDCA on entry into the trial should not initiate UDCA therapy at any time until of the DB treatment period (EOT-DB).

8.1.2. Vaccines

Subjects may receive COVID-19 vaccination or booster during the course of the study. When possible, it should be administered to minimize any disturbance with the interpretation of the safety or efficacy assessment in the study. All COVID-19 vaccinations should be recorded in the concomitant medications.

Live/attenuated vaccines are not allowed within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles/, mumps/rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine.

Killed (inactivated) vaccines used for seasonal influenza or pneumococcal conjugate vaccines are allowed.

8.2. Prohibited Medications

The following medications are prohibited prior to study entry and until the EOT-DB visit:

- Corticosteroids – Must not exceed the equivalent of 10 mg of oral prednisone for at least 28 days prior to subject randomization (Visit 1). Treatment with IV

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corticosteroids within 28 days prior to subject randomization (Visit 1) is not allowed. Topical or inhaled steroids are allowed.

Note: All other IBD treatments need to be on a stable dose for ≥ 12 weeks prior to subject randomization (Visit 1) and be planned to remain on a stable dose through to the EOT-DB visit.

- Antibiotics for treatment of acute cholangitis are not allowed within 90 days prior to subject randomization (Visit 1). Subjects on rotating antibiotics treatment cannot be included into the study.
- NOTE: Antibiotics are permitted, as required, during participation in the trial.
- OCALIVA (Obeticholic Acid; OCA) is not allowed within 12 weeks prior to subject randomization (Visit 1) and through to the EOT-DB visit.
- Investigational agents, other than CM-101, or devices for any indication are not allowed within 60 days prior to subject randomization (Visit 1) and through to the EOT-DB visit. When the study drug half-life is greater than 12 days, at least 5 half-lives need to have passed from the last dose of investigational drug prior to Randomization.
- Any herbal medications other than St. John's Wort or food supplements other than standard vitamin supplements that could potentially interact with the study medication are not allowed within 28 days prior to subject randomization (Visit 1) and through to the EOT-DB visit.

Table 2: List of Prohibited Medications

Drug Class	Requirements
UDCA	Prohibited at doses that exceed 23 mg/kg/day Washout: 12 weeks
Oral or intravenous antibiotics for treatment of acute cholangitis	Prohibited 90 days prior to randomization and during the study
OCALIVA (Obeticholic Acid; OCA)	Prohibited 12 weeks prior to randomization and during the study
Investigational agents, other than CM-101, or devices for any indication	Prohibited 60 days prior to randomization (or at least 5 half-lives if half-life is greater than 12 days) and during the study
Oral prednisone > 10 mg per day or equivalent	Prohibited 28 days prior to randomization and during the study
Intravenous prednisone	Prohibited 28 days prior to randomization and during the study
Live vaccines	Prohibited 30 days prior to randomization and during the study

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Drug Class	Requirements
Herbal medications other than St. John's Wort; food supplements other than standard vitamin supplements	Prohibited 28 days prior to randomization and during the study

Abbreviations: PSC = primary sclerosing cholangitis; TNF = tumor necrosis factor; UDCA = ursodeoxycholic acid.

Medications for disease conditions **excluded** from the protocol (e.g., HIV-1, HBV, or HCV infection, active cancer, transplantation) are not listed under this prohibited medication section and are not allowed in the study.

8.3. Allowed Medications

The intent is to allow all immunosuppressive treatments (e.g., azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline) and other IBD maintenance treatments (e.g., 5-ASA agents) as long as they are not part of the study prohibited medication list, provided the dose has been stable for ≥ 12 weeks prior to subject randomization (Visit 1) and is planned to remain stable throughout the double-blind portion of the trial.

It is acknowledged that signs and symptoms of IBD may worsen or improve during the study and adjustments in medications may be required to provide the subject with the best medical care. Changes in immunosuppressant medications are to be discussed with the Medical Monitor before, or as soon as possible after, administration.

Treatment with fenofibrate or other fibrates is allowed if the subject has been on a stable dose for ≥ 24 weeks prior to Screening and is planned to remain on a stable dose throughout the DB portion of the study.

Treatment with statins is allowed throughout the study without restrictions.

Vancomycin as treatment for PSC is allowed if stable for ≥ 12 weeks before screening.

8.3.1. Therapy for Pruritus

Systemic or enteral therapy for pruritus (e.g., cholestyramine, rifampicin, naltrexone, sertraline) is allowed provided the subject has been on a stable dose for ≥ 12 weeks prior to subject randomization (Visit 1) and is planned to remain on a stable dose throughout the DB portion of the study.

8.3.2. Short-Term Symptomatic NSAID

Acute short-term symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAID) or Paracetamol for symptomatic relief of pain or fever is allowed. Any other acute or chronic medicinal treatments should be discussed with the study medical monitor prior to dosing initiation, if possible.

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8.3.3. Infusion-Related Reactions

Infusion-related reactions are not expected with CM-101; therefore, no premedication is recommended. If infusion-related reactions occur, they can be treated with Paracetamol, NSAIDs, antihistamines, and corticosteroids, or a combination of these.

To date, there is no knowledge of cross reaction between CM-101 and other drugs. It is recommended that changes in ongoing treatments or introduction of new therapies are kept to a minimum to avoid confounding efficacy and safety evaluations.

8.4. Additional Restrictions

Subjects will be instructed not to drink ‘significant amounts’ of alcohol, defined as no more than 14 units/week for both females and males (for the purposes of this study one unit of alcohol is considered to be equal to 8 gr).

Subjects will remain under direct clinical supervision at the clinical research facility for 2 hours after each IP infusion.

8.5. Pregnancy and Contraception

The effects of administration of the IP in pregnant or lactating females or in the developing fetus are unknown. Female subjects of childbearing potential (defined as sexually mature women who have not undergone surgical sterilization or who have not been naturally post-menopausal for at least 24 consecutive months for women ≤ 55 years; for women > 55 years 12 consecutive months) must have a negative serum pregnancy test prior to starting study treatment. Sexually active women of childbearing potential must agree to use a highly effective method of contraception from the Screening Visit throughout the study period including 18 weeks post last dose.

Male subjects must agree to use a barrier method of contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide) or abstinence for the duration of study participation through 90 days after the last dose of the study drug.

Highly effective methods of contraception are considered to be those listed below:

- 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

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- implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy (partner)
- Abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse during the trial duration [from first administration of study drug until 18 weeks post last dose])

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9. SAFETY AND PHARMACOVIGILANCE

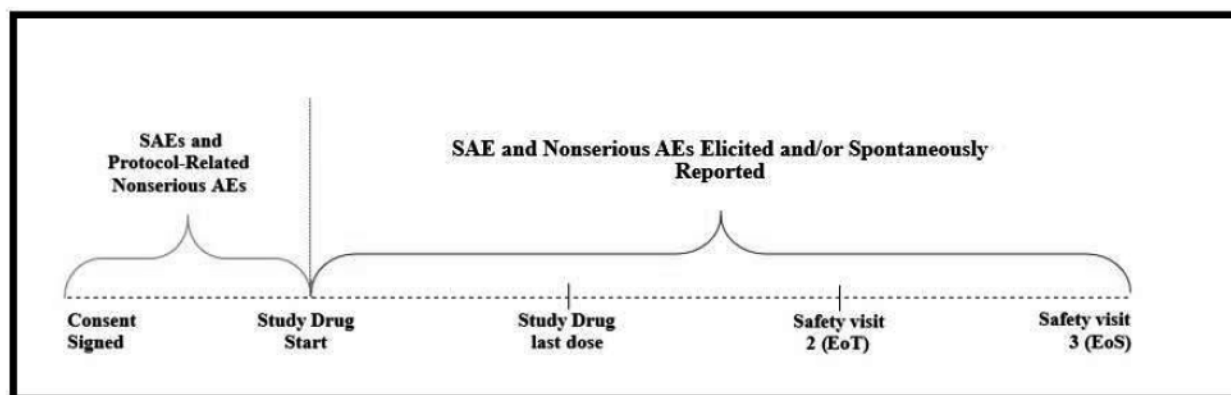
9.1. Adverse Events

An AE is “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” (21CFR312.32, 2015, USA Department of Health and Human Services, September 2010).

An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or seriousness. An AE can arise from any use of the drug (e.g., off-label use, use in combination with other drug) and from any route of administration, formulation, or dose, including an overdose.

An abnormal result of diagnostic procedures including abnormal laboratory results will be considered an AE if it is considered clinically significant in the opinion of the Investigator.

From ICF signing up until the first study drug administration, only SAEs and non-serious protocol-related AEs will be reported in the eCRF. From first study drug administration up until SF3/EOS (Study Day 189 or 420), all AEs reported by the subject or observed by the Investigator will be individually listed on an Adverse Event Form in the eCRF as follows: the specific event or condition, whether the event was present pre-study, the dates and times of occurrence, duration, severity, relationship to study medication, specific counter-measures, and outcome.



Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as AE(s).

Suspected adverse reaction is “any adverse event for which there is a reasonable possibility that the drug caused the adverse event.” Adverse events that are related or possibly related would be suspected adverse reactions; AEs that are not related or unlikely related would not be suspected adverse reactions.

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9.2. Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

- Death;
- Life-threatening; An AE is considered ‘life-threatening’ if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- A persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly or birth defect;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events not considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE;
- Elective treatment for a pre-existing condition that did not worsen;
- Respite care or observation when there is no AE associated with the hospitalization.

9.3. Unexpected Adverse Events

An unexpected adverse drug experience (event) is any adverse event, the specificity or severity of which is not consistent with information in the current Investigator’s brochure for an unapproved IP or package insert/Summary of Product Characteristics for an approved product.

9.4. Suspected Unexpected Serious Adverse Reactions

A SUSAR is a serious adverse reaction assessed as unexpected by the Sponsor and that is judged by either the reporting Investigator or the Sponsor to have a reasonable causal relationship to a medical product. Adverse events that are not related or unlikely related would not be suspected adverse reactions.

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9.5. Anticipated Serious Adverse Events Associated with PSC

Since at this early stage of clinical development the efficacy and safety profile of CM-101 in PSC is unknown, all serious adverse reactions in this clinical study will be considered unexpected for the purpose of safety reporting.

9.6. Grading of Adverse Event Severity

Adverse event severity (Table 3) will be recorded and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (June 14, 2010), and coded into the database according to Medical Dictionary for Regulatory Activities (MedDRA) version 15 or higher. The CTCAE V5.0 manual can be downloaded from the following website:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Table 3: Severity of Adverse Events

Severity	Description ^a
Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Life-threatening	Urgent intervention indicated
Death	Death related to AE

Abbreviations: ADL = activities of daily living; AE = adverse event.

^a A semi- indicates 'or' within the description of the grade.

Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

9.7. Relationship to Study Drug

The Investigator will document, in their medical opinion, the potential event relationship to the IP (study drug) using the criteria outlined in Table 4.

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Table 4: Event Relationship Criteria

Relationship	Criteria
Not related	The temporal sequence of the AE onset relative to administration of the IP is not reasonable. Disease or other drugs provide plausible explanations. Dechallenge (if performed) is negative or ambiguous.
Possibly related	The temporal sequence of the AE onset relative to administration of the investigational is reasonable. Unlikely to be attributed to disease or other drugs. Dechallenge (if performed) is positive.
Related	The temporal sequence of the AE onset relative to administration of the IP is reasonable. Cannot be explained by disease or other drugs. Dechallenge (if performed) is positive and pharmacologically/ pathologically plausible. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the IP or product class, i.e., pharmacologically or phenomenologically recognized/plausible or an objective and specific medical disorder.

Abbreviations: AE = adverse event; IP = investigational product.

If the relationship between an SAE and the IP is determined to be “possibly related”, the event will be considered to be related to the IP for the purposes of expedited regulatory reporting.

9.8. Outcome

The outcome of an AE describes the status of the AE. Definitions for possible outcomes are defined below:

- Recovered: The subject has fully recovered from the AE with no residual effects observable
- Recovered with sequelae: The subject has recovered from the AE with residual effects observable
- Recovering: The subject status improved but has not been fully recovered
- Not recovered (ongoing): The subject status has not recovered from the AE
- Fatal: Termination of life as a result of the AE
- Unknown: Not known, not observed, not recorded, lost for follow-up, or refused

9.9. Reporting of Serious or Unexpected Adverse Events

9.9.1. Initial Notification

Serious AEs that occur from ICF signature up until SF3/EOS Visit (Study Day 420) must be reported by the Investigator via EDC (or via faxed paper form/email communication) to the

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contact person noted below within 24 hours upon learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported SAE must also be reported within 24 hours of the Investigator receiving it.

Additional guidance is provided in the SAE reporting guidelines if the event is reported outside the EDC system.

These preliminary reports will be followed within 24 hours by detailed descriptions that will include a completed SAE form, copies of hospital case reports if applicable, autopsy reports, and other documents, when requested, as applicable.

The following information should be provided in the SAE form to accurately and completely record the event:

- Investigator name and site address
- Subject study identification number
- Subject demographics (gender, date of birth or age, weight, height)
- Clinical Event:
 - Description
 - Date and time of onset, stop date, or duration
 - Intensity
 - Treatment (including hospitalization)
 - Relationship to study drug (causality)
 - Action taken regarding study drug
 - Information on recovery and any sequelae
 - If the SAE resulted in death
 - Cause of death (whether or not the death was related to study drug)
 - Autopsy findings (if available)
 - Medical history case report form (copy)
 - Concomitant medication case report form (copy)
 - Any relevant reports (laboratory, discharge, etc.)
 - Adverse event case report form (copy)

Any newly emergent SAE after treatment is discontinued or the subject has completed the study and is considered to be related to the study drug or study participation should be recorded and reported immediately. The post-study period for the purpose of SAE reporting is up to **30 days following last subject last visit of the study** or until the SAE is resolved or stabilized.

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If an Investigator becomes aware of an SAE that may be attributable to the IP at any time after the end of the study, the Sponsor and/or delegate should be notified immediately (ie, within 24 hours).

The Sponsor and/or delegate will notify the appropriate regulatory agencies as well as all participating Investigators of Investigational New Drug (IND) Safety Reports/Expedited Safety Reports that occur during the trial within the time frames required by each regulatory agency.

For the European Union, the Sponsor and/or delegate will notify the regulatory agencies and report SUSARs via the EudraVigilance database within 7 calendar days of a SUSAR involving death or a life-threatening SUSAR, and all other SUSARs within 15 calendar days.

The Investigator is responsible for submitting Safety Reports/Expedited Safety Reports received from the Sponsor and/or delegate. to the local IRB/IEC, in compliance with the local country requirements.

Documentation of the submissions to IRBs/IECs and health authorities (as applicable) must be retained in the appropriate trial file(s). As instructed by the Sponsor, Safety Reports/Expedited Safety Reports should be retained in the appropriate Investigator site trial files, or with the IB.

9.9.2. Follow-up of Adverse Events

Subjects who have had an AE during the treatment period must be followed up clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained, or until 30 days after the last subject's last visit (whichever is the latest). In exceptional cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

9.10. Management of Drug Induced Liver Injury

Although subjects with underlying chronic liver disease do not appear to have an increased susceptibility for DILI compared with subjects without chronic liver disease (Chalasani, 2004), such cases might happen in this study. This section outlines the assessment, monitoring, and criteria for drug interruption for hepatocellular or cholestatic potential DILI cases (Palmer, 2020).

9.10.1. Hepatocellular DILI

Subjects that experience significant ALT elevation should go through prompt monitoring to evaluate potential development of hepatocellular DILI. Subjects can enter the study with normal or elevated ALT (with a limit of ALT at baseline of $> 5 \times \text{ULN}$). The evaluation, monitoring, and criteria for interruption of study drug treatment for subjects that entered the study with normal or elevated baseline ALT are described in Table 5 and Table 6, respectively. Prior to the decision of drug interruption, ALT should be repeated within 2-5 days to confirm the elevation and change from baseline values. Whenever possible a drug interruption decision should be discussed, in advance, with the study medical monitor.

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Table 5: Criteria for Monitoring and Treatment Interruption for Subjects with Suspected Hepatocellular DILI that Entered the Study with Normal ALT

Treatment-emergent ALT	Bilirubin	Symptoms ^a	Action
ALT $\geq 5 \times$ ULN	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	- Blood tests should be repeated in 2-5 days ^b - Follow-up for symptoms
ALT $\geq 8 \times$ ULN	Normal or elevated	None or present	Interrupt study drug. - Blood tests should be repeated within 2-5 days ^b . Initiate close monitoring and workup for competing etiologies. - Study drug can be restarted only if another etiology is identified, and liver abnormalities return to baseline. - Drug cannot be restarted if hepatic decompensation occurred.
ALT $\geq 3 \times$ ULN	Total bilirubin $\geq 2 \times$ baseline, Gilbert's syndrome or hemolysis: direct bilirubin $> 2 \times$ baseline if baseline > 0.5 mg/dL	None or present	
ALT $\geq 5 \times$ ULN	Normal or elevated	Present	

Abbreviations: ALT = alanine aminotransferase; DILI = drug induced liver injury; ULN = upper limit of normal.

^a Liver-related symptoms (e.g., severe fatigue, nausea, new onset of or worsening of pruritus, right upper quadrant pain); Immunologic reaction (e.g., rash or $> 5\%$ eosinophilia); New onset or increase of pruritus; or hepatic decompensation.

^b The interval between tests should be determined based on the subject's clinical condition.

Table 6: Criteria for Monitoring and Treatment Interruption for Subjects with Suspected Hepatocellular DILI and Elevated Baseline ALT

Treatment-emergent ALT	Bilirubin	Symptoms ^a	Action
ALT $\geq 3 \times$ baseline	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	- Blood tests should be repeated in 2-5-days ^b - Follow-up for symptoms
ALT $\geq 5 \times$ baseline	Normal or elevated	None or present	- Interrupt study drug. - Blood tests should be repeated within 2-5 days ^b . - Initiate close monitoring and workup for competing etiologies. - Study drug can be restarted only if another etiology is identified, and liver abnormalities return to baseline. - Drug cannot be restarted if hepatic decompensation occurred.
ALT $\geq 2 \times$ baseline	Total bilirubin $\geq 2 \times$ baseline Gilbert's syndrome or hemolysis: direct bilirubin $> 2 \times$ baseline if baseline > 0.5 mg/dL	None or present	
ALT $\geq 2 \times$ baseline	Normal or elevated	Present	

Abbreviations: ALT = alanine aminotransferase; DILI = drug induced liver injury; ULN = upper limit of normal.

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^a Liver-related symptoms (e.g., severe fatigue, nausea, new onset of or worsening of pruritus, right upper quadrant pain); Immunologic reaction (e.g., rash or > 5% eosinophilia); New onset or increase of pruritus; or hepatic decompensation.

^b The interval between tests should be determined based on the subject's clinical condition.

Subjects who have developed hepatocellular DILI will be followed for at least 3 months or until a reduction of more than 50% of the peak elevated ALT value is reached.

9.10.2. Cholestatic DILI

Subjects that experience ALP elevation of $2 \times$ baseline without a clear alternative explanation should go through prompt monitoring to evaluate potential development of cholestatic DILI. The evaluation, monitoring, and criteria for interruption of study drug treatment are described in Table 7. Prior to the decision of drug interruption, ALP should be repeated within 7-10 days to confirm the change from baseline value. Whenever possible a drug interruption decision should be discussed, in advance, with the study medical monitor.

Table 7: Criteria for Monitoring and Treatment Interruption for Subjects with Suspected Cholestatic DILI

Treatment-emergent ALT	Bilirubin	Symptoms ^a	Action
ALP $\geq 2 \times$ baseline without alternative explanation	Normal or Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Blood tests should be repeated in 7-10 days ^b . Follow-up for symptoms.
ALP $\geq 2 \times$ baseline without alternative explanation	Total bilirubin $\geq 2 \times$ baseline or Gilbert's syndrome or hemolysis: direct bilirubin $> 2 \times$ baseline if baseline > 0.5 mg/dL	None or present	- Interrupt study drug. - Blood tests should be repeated within 7-10 days^b. - Initiate close monitoring and workup for competing etiologies. - Study drug can be restarted only if another etiology is identified, and liver abnormalities return to baseline. - Drug cannot be restarted if hepatic decompensation occurs.
ALP $\geq 2 \times$ baseline without alternative explanation	Normal or elevated	present	
ALP $\geq 3 \times$ baseline without alternative explanation	Normal or elevated	None or present	

Abbreviations: ALP = Alkaline Phosphatase; DILI = drug induced liver injury; ULN = upper limit of normal.

a. Liver-related symptoms (e.g., severe fatigue, nausea, new onset of or worsening of pruritus, right upper quadrant pain); Immunologic reaction (e.g., rash or > 5% eosinophilia); New onset or increase of pruritus; or hepatic decompensation.

^a Liver-related symptoms (e.g., severe fatigue, nausea, new onset of or worsening of pruritus, right upper quadrant pain); Immunologic reaction (e.g., rash or > 5% eosinophilia); New onset or increase of pruritus; or hepatic decompensation.

^b The interval between tests should be determined based on the subject's clinical condition.

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Subjects who have developed cholestatic DILI will be followed up for 6 months or until their ALP returns to its baseline value or a stabilized reduction was reached.

9.11. Data Monitoring Committee

An independent DMC has been established in order to protect subject welfare, preserve study integrity, and provide recommendations as needed regarding study conduct. The DMC is comprised of at least three external clinician experts in specialties applicable to the diseases under study, as well as a statistician(s). All members of the DMC will have considerable experience with clinical trials and DMC conduct.

The DMC will meet at predefined time points (at least three times per year) and on an as-needed basis based on enrollment, treatment milestones, and safety. The DMC will review safety data from this trial, as well as all ongoing CM-101 trials.

Formal minutes and recommendations will be provided by the DMC to the Sponsor regarding additional data requests and the continuation of the conduct of the study as outlined in the current protocol. The DMC will operate under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization, operation, and specific procedures. The DMC will document, in the closed session DMC minutes (which will be made available to the Sponsor only after the database is locked and the trial is unblinded), details about any unblinded data reviews.

Members of the DMC will be screened for conflicts of interest and any candidate found to have such a conflict will not be offered membership. Conflicts of interest will be assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

Members of the DMC will not be allowed to participate as Investigators in this trial and will not otherwise consult for the Sponsor.

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10. STATISTICAL ANALYSIS

10.1. Sample Size Consideration

A total of 68 adult subjects (age 18-75 years, inclusive) with PSC will be enrolled to the study and randomized to receive either CM-101 (N=50 subjects) at doses of 10 mg/kg or 20 mg/kg or matching placebo (N=18). As the primary outcome measure for this trial is safety, no formal power analyses have been applied. Each dose cohort group size, and thus the overall sample size for the study, is sufficiently large to provide meaningful assessments of the safety and tolerability of each planned CM-101 dose and is consistent with first in patient safety and efficacy trials in PSC. With respect to the secondary outcome measure of relative change from baseline in serum ALP for CM-101 treatment groups compared with placebo and based on two 2-sided independent samples t Tests at an alpha level of 0.025 (to adjust the type 1 error inflation), the planned cohort size of 25 subjects in each CM-101 dose group and placebo cohort size of 18 subjects will provide approximately 81% statistical power to detect a 20% change with a matching 20% standard deviation.

10.2. Analysis Sets

The analysis sets are the following:

- **Intent-to-Treat (ITT) Analysis Set:** The ITT analysis set includes all subjects randomized into the study.
- **Modified Intent-to-Treat (mITT) Analysis Set:** The mITT analysis set includes all randomized subjects who have received at least one dose of CM-101 or placebo.
- **Fifteen-week (15W) Analysis Set:** The 15W analysis set includes all randomized subjects who have completed at least a 15-week treatment period (i.e., completed Treatment 5; Study Day 84) and have no major protocol deviations.
- **Per Protocol (PP) Analysis Set:** The PP analysis set includes all randomized subjects who have completed the 15-week treatment and initial safety follow-up periods (i.e., completed EOT-DB; Study Day 105) and have no major protocol deviations.
- **PK Analysis Set:** The PK analysis set includes all randomized subjects who have received CM-101/placebo treatment and have provided sufficient blood samples for PK evaluation, without relevant deviations interfering with the PK evaluations.

10.3. Handling of Missing Data

The analyses will be based on the data entered into and transferred into the database. Further description of analysis will be described in the Statistical Analysis Plan (SAP).

10.4. Statistical Analysis

All measure variables and derived parameters will be listed individually and if appropriate, tabulated by descriptive statistics.

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For continuous variables, summary tables will be provided giving the number of subjects with data (n), arithmetic mean, standard deviation, median, minimum, and maximum values by treatment group.

For categorical variables, summary tables will be provided giving absolute and relative frequency by treatment group.

Full details of the statistical methodology, analyses, and outputs will be detailed in the SAP. All statistical analyses will be carried out using SAS® Version 9.3 or higher (SAS Institute, Cary North Carolina) under Windows® 2008 Terminal. All tests will be two-tailed, with a significance level of 5%.

10.4.1. Primary Endpoints Analysis

This study has multiple safety-related endpoints, including the frequency and severity of TEAEs, changes in vital signs, changes in clinical safety laboratories, and evaluation of infusion site reactions. Analysis of safety and tolerability endpoints will be compared by CM-101 treatment group and placebo.

The incidence of TEAEs and treatment-emergent SAEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for each treatment group, and similarly by severity and relationship to treatment.

Laboratory parameters and vital signs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The change from Baseline will also be summarized. Electrocardiograms will be summarized by treatment group using frequency at each visit. The shift from baseline will also be summarized.

Adverse event(s) will be coded using the MedDRA (version 15 or higher) terminology for SOC and PT. The number and the percentage of subjects with at least one AE, severe AE, SAE, and AE related to study drug will be summarized by treatment group. Frequency of all AEs, SAEs, and drug-related AEs will be summarized in tables by SOC, PT, and treatment group and by severity. A complete listing of AEs will also be presented sorted by treatment group, and subject number. Additional listing will be generated for SAEs.

Concomitant medications will be coded using World Health Organization (WHO) Drug Reference List, employing Anatomical Therapeutic Chemical (ATC) classifications.

Other safety parameters such as laboratory results, vital signs, ECG, and physical examination will be summarized in appropriate tables.

10.4.2. Secondary Endpoints Analysis

Secondary efficacy analyses of change from baseline through to Week 15 in serum ALP, ELF scores, hepatic biochemistry, and hepatic function parameters will use a Two-Sample t Test for mean difference for comparisons of each CM-101 dose cohort with placebo.

In addition, secondary efficacy analyses of ALP response rates, defined as reduction of ALP to $1.3 \times \text{ULN}$, or a combination of ALP reduction to $1.5\text{--}1.3 \times \text{ULN}$ with an at least 40% reduction from baseline, will compare CM-101 treatment group vs placebo at Week 15 using a

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Cochran-Mantel-Haenszel test. Each CM-101 dose cohort will be compared with placebo in this binary outcome as well.

Categorical improvements or normalization of ALP and liver enzymes will be evaluated using Cochran-Mantel-Haenszel test.

Percent change from baseline over time in liver enzymes (ALT, AST, and GGT) will be analyzed with an analysis of covariance (ANCOVA) model with fixed effects for treatment groups.

Change from baseline in markers of liver fibrosis (e.g., ELF, PRO-C3, PRO-C5) using an ANCOVA model with fixed effects for treatment groups, adjusted for baseline ELF, PRO-C3, and PRO-C5 values, respectively.

Frequency of subjects who developed ADA following repeated CM-101 administration will be summarized in an appropriate table.

10.4.3. Exploratory Endpoints Analysis

The target engagement following repeated administrations of CM-101 (measured by serum CCL24 levels) and other relevant cytokines and chemokines and change over time in serum inflammatory markers, such as hsCRP, MCP1, IL-6, RANTES, will be presented as absolute values and changes as well as relative changes (% change) from baseline to each available visit will be by dose group.

Change from Baseline to Week 15 in liver stiffness using Transient Elastography (preferably Fibroscan) will be presented by dose groups.

Lastly, change from baseline on serum ALP, ELF, liver enzymes, liver fibrosis markers, serum inflammatory markers, and liver elastography to Week 48 will be performed on the subset of subjects who enter the open-label portion of the trial.

10.4.4. Pharmacokinetic Analysis

Compartmental and non-compartmental PK models will be evaluated to determine the pharmacokinetic profile of CM-101. The following PK parameters will be estimated based on the plasma concentrations measured and the PK analysis set:

- C_0 : Pre-dose plasma concentration
- C_{max} : Observed maximum plasma concentration
- T_{max} : Time to reach the observed maximum plasma concentration
- AUC_{last} : Area under the plasma concentration-time curve from time of administration up to the last time point with a measurable concentration post dosing, calculated by linear up-logarithmic down trapezoidal summation.
- AUC_{∞} : Area under the plasma concentration-time curve extrapolated to infinity, calculated as: $AUC_{\infty} = AUC_{last} + C_{last}/\lambda_z$, where AUC_{last} is the last measurable concentration.

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λ_z : Elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve

$T_{1/2}$: Terminal elimination half-life, defined as $0.693/\lambda_z$

Total AUC is calculated by summation of partial AUCs using the trapezoidal rule. An individual segment (AUC₁) is calculated using the following formulation:

$$AUC_1 = (C_0 + C_1) \times \text{Time}_{1-0} / 2$$

Where:

- C_0 is the concentration measured on time 0
- C_1 is the concentration measured on time point 1 (the next time point)
- Time_{1-0} is the time difference between time 1 and time 0.

The total AUC equals a summation of all partial AUC segments.

Summary tables will be provided for the plasma concentration by visit and time and for the PK parameters by visit (day).

Additional parameters may be evaluated based on the PK modeling results.

Individual listings of plasma concentration and PK parameters will be provided.

Graphical displays presenting mean concentration and individual figures by time point will be prepared.

An exposure-response assessment will be made comparing endpoints (such as change in ALP relative to baseline) and serum biomarkers to the average exposure of CM-101 (e.g., AUC or concentration at steady state [C_{ss}]) to help define an optimal dose of CM-101 for this subject population.

10.5. Interim Analyses

Up to 3 interim analyses (IAs) are planned during the conduct of the study. The first IA will be conducted when approximately 14 subjects have completed their Week 15 visit. These IAs will evaluate all safety and tolerability data, as well as PK data. A subset of the PD markers in the study will be analyzed at this time. These prespecified PD measures will be evaluated at baseline, and as a change from baseline at Week 15. Safety data will be assessed to enable the initiation of dosing in the 20 mg/kg dose level cohort. Pharmacokinetic data will be analyzed to confirm exposure; interpatient variability and effect sizes on the study outcome measures will be analyzed in order to inform study dose level cohort sample sizes. The safety, PK, and PD data listings provided to the DMC will not contain subject identification numbers or any other unblinding treatment information; however, the DMC may ask to unblind an individual subject and/or group data, as appropriate. The Sponsor or any designee (except for the Sponsor's unblinded personnel), subjects, Investigator(s), and trial site staff will remain blinded to treatment allocations during the interim data analysis and will not participate in the DMC closed

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session discussion. Trial recruitment will continue during the interim data collection and analysis.

A second unblinded IA will occur when all subjects complete the double-blind portion of the study through Week 15. The IA will evaluate all available safety, tolerability, PK, and PD and efficacy data from all cohorts in the study. Dosing in the open-label portion of the study will continue during the IA data collection and analysis.

A separate SAP will be generated for the IA data, describing the conduct of the IA in detail.

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11. REGULATORY REQUIREMENTS

11.1. Independent Ethics Committee

Prior to initiation of the study, the Principal Investigator will submit the study protocol and amendments, sample ICF, Subject Information Sheet (PIS), and any other documents that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. The Investigator will not begin the study until the protocol and ICF/PIS have been approved by the IRB/IEC. The Investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening conditions, or death.

11.2. Ethical Conduct of the Study

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with Sponsor's and delegate standards operating procedures and the following guidelines:

- ICH – GCP
- Declaration of Helsinki
- FDA 21 CFR 50.25
- Israeli Guidelines, Laws, and Regulations for the conduct of clinical trials

11.3. Protocol Revisions and/or Deviations

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements and, if required, to Regulatory Agencies, either as an amendment or a notification. Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval will be required for notifications.

11.4. Subject Information and Consent

Prior to screening for the study each subject will be informed in detail about the study drug to be administered and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. Written consent will be obtained from each subject to be involved in the clinical trial by using the IRB/IEC-approved ICF (or Patient Information Sheet) prior to the

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conduct of any study-related activity. Each subject will be given a copy of the signed ICF. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Each subject's chart will include the original signed ICF for study participation. The ICF will be kept in the Investigator's central study file for the required period of time. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study. If the ICF is modified during the study, in a way that can affect the subject judgment to participate, all subjects still ongoing will be re-consented and the original re-consent forms will be included in the subject's chart.

11.5. Insurance

The Sponsor has an insurance policy for the total duration of the study covering the subjects and Investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's file or can be made available to the Investigator and to the IRB/IEC upon request.

11.6. Informing the General Practitioner

The Investigator will inform the subject's primary care physician of his participation in the study, by sending a letter to the physician if required by the local authorities and only upon the request of the subject.

11.7. Personal Data Protection

The Sponsor complies with the principle of subject's right to protection against invasion of privacy. Throughout this trial, all data will be identified only by an identification number and subject initials. The data will be blinded in all data analyses. The subject must be informed, and written consent is required that authorized personnel of the Sponsor and/or designee (Study Monitor, Auditor, Clinical Research Organization (CRO), Sponsor's Strategic Partner, etc.) and relevant health regulatory agency, including outside of Israel, may have direct access to personal medical data to assure a high-quality standard of the study, and/or to obtain regulatory approvals. The data will be de-identified where appropriate and consistent with study needs.

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12. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the eCRF or ultimately transferred into the database to ensure accuracy and completeness.

Training sessions, regular monitoring of the trial at the trial site by the Sponsor or designated personnel (e.g., CRA), instruction manuals, data verification, cross checking, and data audits will be performed to ensure quality of all trial data. Investigators' meetings and/or onsite trial initiations will be performed to prepare Investigators and other trial site personnel for appropriate collection of trial data.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor and/or delegate may conduct a quality assurance audit.

The Sponsor and/or delegate maintains a quality assurance system with written standard operating procedures (SOPs) to ensure that clinical trials are conducted, and data is generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

12.1. Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor Quality Assurance or its designees or to regulatory authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study and are based on the national regulations, as well as ICH guidelines.

12.2. Study Monitoring

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO or a contract monitor. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements. Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRF will be reviewed for completeness with corresponding source documents. As part of the data audit, source documents must be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the Investigator's study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The Investigator or appointed delegate will receive the study monitor during these on-site visits; cooperate in providing the documents for inspection and respond to inquiries.

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12.3. Source Document

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents whether they are in paper or electronic form. Source documents are original records in which raw data is first recorded. These may be office/clinic/hospital records, charts, diaries, x-rays and laboratory results, printouts, pharmacy records, care records, completed scales for each study participant. Source documents should be kept in a secure and limited access area. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. The subject study file should contain all relevant historic and contemporary records in a permanent form of recording (ink, typing, printing, optical disc etc.). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for subjects registered to the study should indicate date informed consent was signed, participation in clinical protocol number and title, treatment number, evidence that inclusion/exclusion criteria have been met.

12.4. Quality Laboratory Standards

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the laboratory or central laboratories.

12.5. Data Management

A data management plan will be prepared by the Sponsor and/or its designated representative.

Various edit checks will be performed for the purpose of ensuring the accuracy, integrity and validity of the database. These edit checks may include:

- Missing value checks
- Range checks
- Consistency checks
- Sequence checks
- Probabilistic checks
- Protocol adherence checks

Queries generated from these checks will be sent to the investigational site for resolution and the database will be updated to reflect query resolutions as appropriate.

Adverse events will be coded using the MedDRA (version 15 or higher). Prior and concomitant medications will be coded according to the WHO Drug Dictionary Enhanced March 2015 or higher.

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13. STUDY ADMINISTRATION

13.1. Required Documents Prior to Study Initiation

Prior to the start of this study, all pre-investigational requirements must be met by the Investigator and study sites. These may include but are not limited to:

- Appropriate local health authority documentation properly signed and dated by the required Investigators (i.e., the submission package)
- Signed copy (original) of the approved protocol signature page
- Completed and signed statement of Investigator
- A signed Clinical Trial Agreement
- Current Curriculum vitae for the Investigator and sub-Investigators which are signed stamped by the Investigator
- Laboratory certification and reference ranges
- IRB/IEC name and address, and membership list or number.
- Letter of approval or favorable opinion (as appropriate) given by the IRB/IEC for protocol (identified by protocol title and number), and all versions and languages of ICFs and/or subject information sheets (identified by protocol title and number)
- Copy of the IRB/IEC-approved written ICF/PIS to be used in the study (that has also been approved by the Sponsor)
- Provisions for direct access to source/data documents, if necessary, for trial-related monitoring, audits, IRB/IEC review and regulatory inspection

The Investigator is also responsible for providing the IB and any other available safety information and information about payments and compensation available to trial subjects to the independent ethics committee for review.

Upon satisfactory receipt of all required regulatory documents, Sponsor and/or delegate will arrange that study drugs be delivered to the study site. Supply of all other study materials will be the responsibility of the Sponsor and/or designee. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo training to include review of study protocol, instructions for eCRF completion, AE reporting and overall responsibilities including those for drug accountability and study file maintenance.

The Investigator and/or designee will prepare an Investigator's study file. This file should be used for all trial related documents. The Investigator will be responsible for keeping the Investigator's file updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

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The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. The protocol must be reapproved by the IRB/ IEC upon receipt of amendments and/or annually, as local regulations require. A favorable opinion on substantial amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to trial participants. In addition, the IRB/ IEC must approve all advertising used to recruit subjects for the trial.

Progress reports and notifications of safety issues will be provided to the IRB/IEC according to local regulations and guidelines. Investigators or the Sponsor or appropriate designees will provide reports to the IRB/IEC as requested, as a minimum annually, and after the trial is complete.

13.2. Clinical Trial Supplies

The Sponsor and/or designated representative will be responsible for supplying clinical trial supplies. The Investigator will be responsible for inventory and accountability of all clinical trial supplies at his/her site, exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study the Investigator will keep a copy of the inventory record, destruction record (if relevant) and a record of the clinical supplies returned. Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol.

Clinical trial supplies include, however, are not limited to study drugs.

13.3. Investigator Site File

The Investigator's site file will be provided by the Sponsor and/or delegate up to the initiation visit. All documents required for the conduct of the study as specified in the ICH GCP guidelines will be maintained by the Investigator in an orderly manner in the Investigator's site file and made available for monitoring and/or auditing by the Sponsor and/or delegate and regulatory agencies.

13.4. Study Completion

This study is expected to end after all enrolled subjects have completed the EOS visit.

Data and materials that are required for the study to be considered complete and/or terminated are:

- Laboratory findings, clinical data, and all special test results from screening through to the end of the follow-up period
- eCRF properly completed by appropriate study personnel and signed by the Investigator
- Completed Drug Accountability Records

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- Statement of outcome for each serious adverse event reported to the Sponsor and/or delegate and IRB/IEC
- Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable)

All collected data whether it is in paper or electronic form must be reviewed, signed, and dated by the Investigator or appropriate designee before study completion.

13.5. Final Report

A final study report will be prepared by the Sponsor or designee upon completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

13.6. Retention of Study Records

The Investigator will retain copies of the approved protocol, copy pages of the completed eCRFs, informed consent documents, relevant source documents and all other supporting documentation related to the project per country specific regulations, and for no less than until 2 years after the approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor. The Sponsor and/or delegate will inform Investigators should it become aware of any changes in storage requirements.

If the Investigator is unable to retain the study documents for the required amount of time or if responsibility for the trial site is transferred, Sponsor or designee must be consulted for assistance and informed of the individual who will be assuming this responsibility.

These files must be made available for inspection upon reasonable request by authorized representatives of Sponsor and/or the relevant regulatory agencies.

At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor prior to the destruction of any records.

13.7. Confidentiality and Publication

Subject medical information obtained by the study is confidential and disclosure to third parties other than those noted below in this section is prohibited. Throughout the study, all data will be identified only by the subject identification number and where applicable, the subject's initials and birthdates.

Subject to, and dependent upon, the subject's written request, Subject medical information from the Study may be given to his or her personal physician or other appropriate medical personnel responsible for his welfare. In accordance with local regulations, when appropriate, the personal physician of the study participant will be notified by the Investigator of subject participation in the study.

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All information supplied by the Sponsor and/or delegate, in association with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, the protocol, eCRFs and other scientific data. Any data collected during the study is also considered confidential.

This confidential information shall remain sole property of the Sponsor, shall not be disclosed to others without the prior written consent of the Sponsor and shall not be used except in the performance of this study.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Table 8: Schedule of Assessments - Double-Blind Treatment Period

Study Part	Screening	Double-Blind Treatment Period							Safety Follow-up ¹ (Non-OL Subjects Only)	
Visit	Screening	V1	SF1	V2	V3	V4	V5	V6	V7	V8
Visit Title		Treatment 1 ²	Safety Visit 1	Treatment 2 ²	Treatment 3 ²	Treatment 4 ²	Treatment 5 ²	EOT-DB ^{3,4} SF2 or OL Treatment 1	FU Call	SF3/EOS
Study Day ⁵	[-42, 0]	0	7	21	42	63	84	105	147	189
Week	[-6, 0]	0	1	3	6	9	12	15	21	27
Informed consent signature	X							X ⁶		
Inclusion/Exclusion criteria	X	X						X ⁶		
Demographic data	X									
Medical history review	X									
Record prior/concomitant medications	X	X	X	X	X	X	X	X	X	X
Record AEs	X ⁷	X	X	X	X	X	X	X	X	X
Complete physical examination ⁸	X	X						X		X
Targeted physical examination ⁸			X	X	X	X	X			
Weight, BMI ⁹	X	X		X	X	X	X	X		
Height	X									
Vital signs ¹⁰	X	X	X	X	X	X	X	X		X
12-Lead ECG	X	X			X			X		
Pregnancy test ¹¹	X	X		X	X	X	X	X		
Safety blood tests ¹²	X	X	X	X	X	X	X	X		
Urinalysis ¹³	X	X						X		
Liver enzyme measurements ¹⁴	X	X	X	X	X	X	X	X		

Study Part	Screening	Double-Blind Treatment Period							Safety Follow-up ¹ (Non-OL Subjects Only)	
Visit	Screening	V1	SF1	V2	V3	V4	V5	V6	V7	V8
Visit Title		Treatment 1 ²	Safety Visit 1	Treatment 2 ²	Treatment 3 ²	Treatment 4 ²	Treatment 5 ²	EOT-DB ^{3,4} SF2 or OL Treatment 1	FU Call	SF3/EOS
Study Day ⁵	[-42, 0]	0	7	21	42	63	84	105	147	189
Week	[-6, 0]	0	1	3	6	9	12	15	21	27
Lipid profile ¹⁵		X ¹⁵			X ¹⁵		X ¹⁵			
Coagulation tests ¹⁶	X	X						X		
Serology	X									
Transabdominal Ultrasound	X									
Transient Elastography ¹⁷	X							X		
Randomization DB		X								
OL Drug Assignment								X ⁶		
Study drug administration ^{18 19}		X1		X2	X3	X4	X5	X ⁶		
Infusion site reaction evaluation ²⁰		X	X	X	X	X	X	X		
PK samples ²¹ (pre/post dose only) ²²		X	X	X	X	X	X	X		X
PD samples ^{22 23 24 25}		X	X	X	X	X	X	X		X
Immune cell sub populations ^{22 26}		X			X			X		
IgG4 & IgG1		X			X			X		
Plasma Bile Acids & C4		X			X		X	X		
Ca 19-9 Blood Test ²⁷	X									
Pruritus 5-D ²⁸	X	X		X	X	X	X	X		
Fatigue Severity Scale ²⁸	X	X		X	X	X	X	X		
CDAI or Partial Mayo scoring ²⁹		X	X	X	X	X	X	X		
Immunogenicity (ADA) ³⁰		X			X			X ⁶		X

Study Part	Screening	Double-Blind Treatment Period							Safety Follow-up ¹ (Non-OL Subjects Only)	
Visit	Screening	V1	SF1	V2	V3	V4	V5	V6	V7	V8
Visit Title		Treatment 1 ²	Safety Visit 1	Treatment 2 ²	Treatment 3 ²	Treatment 4 ²	Treatment 5 ²	EOT-DB ^{3,4} SF2 or OL Treatment 1	FU Call	SF3/EOS
Study Day ⁵	[-42, 0]	0	7	21	42	63	84	105	147	189
Week	[-6, 0]	0	1	3	6	9	12	15	21	27
Liver tissue biopsy	X ³¹									

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMI = body mass index; CBC = complete blood count; CDAI = Crohn's Disease Activity Index; DB = double-blind; ECG = electrocardiogram; ELF = enhanced liver fibrosis; EoI = end of infusion; EOS = end of study; EOT = end of treatment; FU = follow-up; GGT = gamma glutamyl transferase; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; ICF = informed consent form; IgG = immunoglobulin G; IV = intravenous; LDL = low-density lipoprotein; OL = open-label; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; SF = safety visit; SOA = Schedule of Assessments; V = visit.

¹ Subjects who choose not to participate in the OL treatment portion will complete the Safety Follow-up Call (Study Day 147) and EOS (Study Day 189) visits.

² Each treatment visit will be followed by a Safety phone Call 3 days after study drug administration (i.e., on Study Days 3, 24, 45, 66, and 87; ± 1 day window). SF1 and SF3/EOS visits and Visits 2-5 can be done at home or a pre-designated off-site location, only in the extreme case in which the subject cannot reach the study site. In that case, the maximal number of assessments must be performed.

³ For subjects who choose not to participate in the OL treatment portion, this visit will serve as the SF2/EOT visit. For eligible subjects who continue into the OL treatment portion, this EOT-DB visit will be considered the OL Treatment 1 Visit.

⁴ Subjects who discontinue prematurely from the study should complete the Safety Follow-up Period visits (Visits 17, 18, and 19) listed under the OL Treatment SOA and perform all assessments as described for the SF2/EOT visit at Week 48 (Study Day 336), the Safety Follow-up Call at Week 54 (Study Day 378), and the SF3/EOS visit at Week 60 (Study Day 420).

⁵ The allowed time period for all treatment/safety visits is ± 3 days, except to SF1 the allowed time period is ± 1 day and for SF3/EOS the allowed time period is ± 7 days.

⁶ For subjects who continue into the OL treatment portion only.

⁷ From ICF signature up until the first study drug administration, only SAEs and protocol-related non-serious AEs reported by the subject or observed by the Investigator will be recorded.

⁸ Physical examinations on treatment days will be performed pre- and post-dose. A complete physical examination will be performed at Screening and Visits 1, 6, and 8. Targeted physical examinations (history and symptom directed) will be performed at the other time points listed in the SOA.

⁹ Weight and BMI calculations will be done before every study drug administration and at the SF2/EOT visit.

¹⁰ Vital signs: supine blood pressure, supine heart rate, respiration rate (RR), and body temperature (oral or tympanic); at Screening only, an additional standing blood pressure test will be done to rule out orthostatic hypotension. On treatment days, vitals will be recorded prior to dosing (within 90 minutes before dosing), 2 hours post dosing (± 15 min) and prior to discharge (if discharge is later than 2 hours post dosing).

¹¹ For females of childbearing potential only. Pregnancy testing is not required for post-menopausal or surgically sterilized women (per subject records). At Screening, a serum β -human chorionic gonadotropin (β -hCG) pregnancy test will be done. On subsequent visits, either a urine or serum test can be used (if urine test results are inconclusive or positive, the test must be repeated in serum).

- ¹²Safety laboratory tests will include Biochemistry and CBC. Blood for safety laboratory assessments will be collected pre-dose at all study site visits (Screening, V1-V17, SF1, and SF2/EOT) and post dose on Visit 1 (Treatment 1) only.
- ¹³Urinalysis will be done pre-dose at specified visits either laboratory -based or via dipstick.
- ¹⁴Liver enzyme measurement tests will include ALT, AST, GGT, ALP, and total bilirubin.
- ¹⁵Lipid profile (total cholesterol, LDL, HDL, and triglyceride) will be done after a 10-hour fast.
- ¹⁶Coagulation tests will be done at Screening, pre-dose at Visit 1 (Treatment 1), and at the SF2/EOT (Study Day 105).
- ¹⁷Transient Elastography (preferably Fibroscan™) will be performed up to 5 days from the SF2/EOT visit (Study Day 105) per scheduling availabilities. Both assessments (Screening and SF2/EOT) must be performed with the same device model.
- ¹⁸In case the prescription is sent to the pharmacy prior to the subject weight measurement, for dose calculation purposes, the weight measurement from the previous visit can be used instead. Subjects will not be allowed food or drink (other than water) during drug administration and until 1 hour post end of drug administration. There is no limitation on drinking water.
- ¹⁹A Safety Follow-up Call will be conducted 3 days after each study drug administration (i.e., on Study Days 3, 24, 45, 66, and 87; ± 1 day window).
- ²⁰Local site reactions will be assessed at each dosing visit (V1-V16) at 2 hours $\pm$ 20 minutes after dosing and during Safety visits 1 and 2 (SF1 and SF2/EOT) and/or at SF3/EOS if done prior to Week 15 or Week 48.
- ²¹Blood for PK testing will be drawn pre-dose on each DB treatment day, within 90 minutes prior to study drug administration, and during all safety follow-up visits (SF1, Study Day 7; SF2/EOT, Study Day 105; SF3/EOS, Study Day 189). At Treatments 1 and 5 (Study Days 0 and 84), blood will also be drawn for PK testing at EoI (time=0 hours), and at 2 hours post EoI (all post infusion blood draws are within ± 10 min of the assigned time point).
- ²²The IV line used for drug administration will not be used for PK and other blood draws. It is recommended that it will be removed once the infusion has been completed.
- ²³PD samples include [REDACTED], and serum inflammatory markers (hsCRP, MCP1, IL-6, RANTES and IL-1).
- ²⁴Serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES and IL-1) will be performed by a central laboratory; see Appendix 2 for more information.
- ²⁵Blood for PD testing will be drawn within 90 minutes pre-dose and at 2 hours (± 10 minutes) post EoI on each dosing day. During the SF1, SF2/EOT-DB (Study Days 7 and 105), and SF3/EOS (Study Day 189) visits, samples will be taken during the visit.
- ²⁶Immune cell subpopulations (whole blood) samples will be taken in selected countries/sites pre-dose within 90 minutes before dosing at specified visits and during the SF2/EOT visit (Study Day 105).
- ²⁷Only for subjects with no test results within 12 months prior to screening.
- ²⁸The Pruritus 5-D itch scale and the Fatigue Severity Scale questionnaires should be completed by the subject at the beginning of each of the following visits: Screening, at each treatment visit, and at the SF2/EOT visit.
- ²⁹Only for subjects with IBD, if IBD status worsened.
- ³⁰Blood sampling for immunogenicity (anti-CM-101 antibodies) will be taken on Visit 1 (Treatment 1; Study Day 0) pre-dose (within 90 minutes before dosing), Visit 3 (Treatment 3; Study Day 42) pre-dose (within 90 minutes before dosing), SF2/EOT (Study Day 105), and SF3/EOS (Study Day 189) during the visit.
- ³¹Collect if available stored tissue from recent biopsy in prior 12 months.

Table 9: Schedule of Assessments - Open-Label Treatment Period and Safety Follow-up Period

Study Part	Open-label Treatment Period										Safety Follow-up/ET ¹ (Open-label Subjects Only)		
Visit	V7 ²	V8 ²	V9 ²	V10 ²	V11 ²	V12 ²	V13 ²	V14 ²	V15 ²	V16 ²	V17	V18	V19
Visit Title	OL Tx 2	OL Tx 3	OL Tx 4	OL Tx 5	OL Tx 6	OL Tx 7	OL Tx 8	OL Tx 9	OL Tx 10	OL Tx 11	EOT-OL ³ (SF2)	FU Call	SF3/ EOS
Study Day ⁴	126	147	168	189	210	231	252	273	294	315	336	378	420
Week	18	21	24	27	30	33	36	39	42	45	48	54	60
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination ⁵					X						X		X
Targeted physical examination ⁵	X	X	X	X		X	X	X	X	X			
Weight, BMI ⁶	X	X	X	X	X	X	X	X	X	X	X		
Vital signs ⁷	X	X	X	X	X	X	X	X	X	X	X		X
12-Lead ECG					X						X		
Pregnancy test ⁸	X	X	X	X	X	X	X	X	X	X	X		
Safety blood tests ⁹	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis ¹⁰											X		
Liver enzyme measurements ¹¹	X	X	X	X	X	X	X	X	X	X	X		
Lipid profile ¹²					X						X		
Coagulation tests ¹³					X						X		
Transient Elastography ¹⁴											X		
IP administration ^{15, 16}	OLX2	OLX3	OLX4	OLX5	OLX6	OLX7	OLX8	OLX9	OLX10	OLX11			
Infusion site reaction evaluation ¹⁷	X	X	X	X	X	X	X	X	X	X	X		
PK samples ^{18, 19}		X			X			X			X		X
PD samples ^{19, 20, 21, 22}		X			X			X			X		X
Immune cell sub populations ^{19, 23}					X						X		

Study Part	Open-label Treatment Period										Safety Follow-up/ET ¹ (Open-label Subjects Only)		
Visit	V7 ²	V8 ²	V9 ²	V10 ²	V11 ²	V12 ²	V13 ²	V14 ²	V15 ²	V16 ²	V17	V18	V19
Visit Title	OL Tx 2	OL Tx 3	OL Tx 4	OL Tx 5	OL Tx 6	OL Tx 7	OL Tx 8	OL Tx 9	OL Tx 10	OL Tx 11	EOT-OL ³ (SF2)	FU Call	SF3/ EOS
Study Day ⁴	126	147	168	189	210	231	252	273	294	315	336	378	420
Week	18	21	24	27	30	33	36	39	42	45	48	54	60
IgG4 & IgG1					X						X		
Plasma Bile Acids & C4					X						X		
Pruritus 5-D ²⁴					X						X		
Fatigue Severity Scale ²⁵											X		
CDAI or Partial Mayo scoring ²⁶											X		
Immunogenicity (ADA) ²⁷					X						X		X
Liver tissue biopsy									X ²⁸				

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BMI = body mass index; CBC = complete blood count; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; ELF = enhanced liver fibrosis; EoI = end of infusion; EOS = end of study; EOT = end of treatment; ET = Early Termination; FU = follow-up; GGT = gamma glutamyl transferase; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; IgG = immunoglobulin G; IV = intravenous; LDL = low-density lipoprotein; OL = open-label; PD = pharmacodynamic; PK = pharmacokinetic; SF = safety visit; SOA = Schedule of Assessments; TX = treatment; V = visit.

¹ Subjects who discontinue prematurely from the study should complete the Safety Follow-up Period visits (Visits 17, 18, and 19) listed under the OL Treatment SOA and perform all assessments as described for the SF2/EOT visit at Week 48 (Study Day 336), the Safety Follow-up Call at Week 54 (Study Day 378), and the SF3/EOS visit at Week 60 (Study Day 420).

² Each treatment visit will be followed by a Safety phone Call 3 days after study drug administration (i.e., on Study Days 129, 150, 171, 213, 234, 255, 276, 297, and 318 ± 1 day window). Visits 7-16 and the SF3/EOS visit can be done at home or a predesignated off-site location, only in the extreme case in which the subject cannot reach the study site. In that case, the maximal number of assessments must be performed.

³ For eligible subjects who continue into the OL treatment portion, this visit will serve as the SF2/EOT Visit.

⁴ The allowed time period for all OL treatment visits is ± 3 days, except to SF3/EOS the allowed time period is ± 7 days.

⁵ Physical examinations on treatment days will be performed pre- and post-dose. Complete physical examinations will be performed at Visits 11, 17, and 19. Targeted physical examinations (history and symptom directed) will be performed at the other time points listed in the SOA.

⁶ Weight and BMI calculations will be done before every study drug administration and at the SF2/EOT-OL visit.

⁷ Vital signs: supine blood pressure, supine heart rate, respiration rate (RR), and body temperature (oral or tympanic). On all OL treatment days, vitals will be recorded prior to dosing (within 90 minutes before dosing), 2 hours post dosing (± 15 min) and prior to discharge (if discharge is later than 2 hours post dosing).

- ⁸ For females of childbearing potential only. Pregnancy testing is not required for post-menopausal or surgically sterilized women (per subject records). At Screening, a serum β -human chorionic gonadotropin (β -hCG) pregnancy test will be done. On subsequent visits, either a urine or serum test can be used (if urine test results are inconclusive or positive, the test must be repeated in serum).
- ⁹ Safety laboratory tests will include Biochemistry and CBC. Blood for safety lab assessments will be collected pre-dose at all study site visits (Screening, V1-V17, SF1, and SF2/EOT) and post dose on Visit 1 (Treatment 1) only.
- ¹⁰ Urinalysis will be done pre-dose at specified visits either laboratory-based or via dipstick.
- ¹¹ Liver enzyme measurement tests will include ALT, AST, GGT, ALP, and total bilirubin.
- ¹² Lipid profile (total cholesterol, LDL, HDL, and triglyceride) will be done after a 10-hour fast.
- ¹³ Coagulation tests will be done at Visit 11 (OL Treatment 6), and at the SF2/EOT-OL (Study Day 336).
- ¹⁴ Transient Elastography (preferably Fibroscan™) will be performed up to 5 days from the SF2/EOT-OL visit (Study Day 336) per scheduling availabilities. Both assessments (Screening and SF2/EOT) must be performed with the same device model.
- ¹⁵ In case the prescription is sent to the pharmacy prior to the subject weight measurement, for dose calculation purposes, the weight measurement from the previous visit can be used instead. Subjects will not be allowed food or drink (other than water) during drug administration and until 1 hour post end of drug administration. There is no limitation on drinking water.
- ¹⁶ A Safety Follow-up Call will be conducted 3 days after each study drug administration (i.e. on Study Days 129, 150, 171, 213, 234, 255, 276, 297, and 318; $\pm$ 1 day window).
- ¹⁷ Local site reactions will be assessed at each dosing visit (V1-V16) at 2 hours $\pm$ 20 minutes after dosing and during the SF2/EOT (Study Day 336) and/or at SF3/EOS if done prior to Week 48.
- ¹⁸ Blood for PK testing will be drawn pre-dose within 90 minutes prior to IP administration, at the EoI (time=0)*, and at 2 hours post EoI at Visits 8, 11, and 14 (OL Treatments 3, 6, and 9; Days 147, 210, and 273) and a single assessment during the safety follow-up visits (SF2/EOT, Study Day 336; SF3/EOS, Study Day 420).
- ¹⁹ The IV line used for drug administration will not be used for PK and other blood draws. It is recommended that it will be removed once the infusion has been completed.
- ²⁰ PD samples include [REDACTED], and serum inflammatory markers (hsCRP, MCP1, IL-6, RANTES and IL-1).
- ²¹ Serum inflammatory markers (e.g., hsCRP, MCP1, IL-6, RANTES and IL-1) will be performed by a central laboratory; see Appendix 2 for more information.
- ²² Blood for PD testing will be drawn within 90 minutes pre-dose and at 2 hours ($\pm$ 10 min) post EoI at V8, V11, and V14. During the safety follow-up visits (SF2/EOT, Study Day 336; SF3/EOS, Study Day 420), samples will be taken during the visit.
- ²³ Immune cell subpopulations (whole blood) samples will be taken in selected countries/sites pre-dose within 90 minutes before dosing at specified visits and during the SF2/EOT visit (Study Day 336).
- ²⁴ The Pruritus 5-D itch scale questionnaire should be completed by the subject at the beginning of the Visit 11 (OL Treatment 6) and at the SF2/EOT visit (Study Day 336).
- ²⁵ The Fatigue Severity Scale questionnaire should be completed by the subject at the beginning of the SF2/EOT visit (Study Day 336).
- ²⁶ Only for subjects with IBD, if IBD status worsened.
- ²⁷ Blood sampling for immunogenicity (anti-CM-101 antibodies) will be taken on Visit 11 (OL Treatment 6) pre-dose (within 90 minutes before dosing) and during the SF2/EOT (Study Day 336) and SF3/EOS (Study Day 420) visits.
- ²⁸ If historic tissue was available for subject at Screening, then optionally collect for comparison.

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APPENDIX 2. LOCAL AND CENTRAL LABORATORY TEST PARAMETERS

LOCAL LABORATORY	
Serum Biochemistry Total Protein Albumin LDH Creatinine Phosphokinase Glucose Sodium Potassium BUN or Urea Creatinine Calcium Phosphate Lipid Profile (total cholesterol, LDL, HDL, and triglyceride)	Haematology Red Blood Cell Count Hemoglobin (HGB) Hematocrit (HCT) Mean Cell Hemoglobin Mean Cell Hemoglobin Concentration Mean Corpuscular Volume White Blood Cell Count and Differential Platelet Count
Liver Enzyme Measurements ALT AST GGT Alkaline phosphatase Total bilirubin	Urinalysis (either lab-based or dipstick) Protein Nitrates Glucose Specific Gravity Ketones Urobilinogen Bilirubin pH Blood (Hemoglobin) Leukocytes
Coagulation Tests Prothrombin Time Activated partial thromboplastin time INR	Serology HIV Ab HBS Ag HCV Ab IgG1 IgG4
Pregnancy Tests Serum (only required at Screening) Urine	Ca 19-9 Blood Test (to be done only for subjects with no test results within 12 months prior to screening)

Abbreviations are located on the next page.

CENTRAL LABORATORY:

Serum Bile Acids and C4 (7 α -hydroxy-4-cholesten-3-one)

Serum Inflammatory Markers

hsCRP

MCP1

IL-6

RANTES

IL-1

Immune Cell Sub Population (whole blood)

PK Assessments

PD Assessments

Anti-Drug Antibodies (ADA)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ca 19-9 = cancer antigen 19-9; CCL24 = chemokine (C-C motif) ligand 24; ELF = enhanced liver fibrosis; GGT = gamma glutamyl transferase; HBSAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HDL = high-density lipoprotein; HIV Ab = human immunodeficiency virus antibody; hsCRP = high-sensitivity C-reactive protein; IgG = immunoglobulin G; IL = interleukin; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCP1 = monocyte chemoattractant protein 1; PD = pharmacodynamic; PK = pharmacokinetics; [REDACTED]; RANTES = regulated on activation, normal T cell expressed and secreted.

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APPENDIX 3. PARTIAL MAYO SCORING SYSTEM FOR ASSESSMENT OF ULCERATIVE COLITIS ACTIVITY

Partial Mayo Scoring System for Assessment of Ulcerative Colitis Activity (The Partial Mayo Score Ranges from 0-9, with higher scores indicating more severe disease)
Stool Frequency (Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency) 0 = Normal no. of stools for this subject 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal Subscore: 0 to 3
Rectal Bleeding* (The daily bleeding score represents the most severe bleeding of the day) 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes Subscore: 0 to 3
Physician's Global Assessment (This assessment acknowledges the two other criteria, the subject's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status) 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease Subscore: 0 to 3

*Assigning a score of 3 requires subjects to have $\geq 50\%$ of bowel movement accompanied by visible blood and 1+ bowel movement with blood alone.

Primary reference: (Schroeder, 1987).

Validation: (Travis, 2013).

Score interpretation:

- The higher the score, the more severe the case of ulcerative colitis.
- The highest score possible is a 12.
- Scores should be compared to previous scores taken for a subject.
- The mucosal appearance at endoscopy is not included in the Partial Mayo Score.

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APPENDIX 4. CROHN'S DISEASE ACTIVITY INDEX

Clinical or Laboratory Variable	Answer	Weighting factor
Number of liquid or soft stools each day for seven days (<i>sum</i>)		× 2
Abdominal pain (graded from 0-3 on severity) each day for seven days (<i>Average daily rating</i> × 7)	0 = None 1 = Mild 2 = Moderate 3 = Severe	× 5
General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days (<i>Average daily rating</i> × 7)	0 = Generally well 1 = Slightly under par 2 = Poor 3 = Very poor 4 = Terrible	× 7
Presence of extra intestinal/physical complications* (<i>Sum</i>)	0 = No, 1 = Yes*	× 20
Taking Lomotil or opiates for diarrhea (antidiarrheal drug use in previous 7 days)	0 = No 1 = Yes	× 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	0 = No 2 = Questionable 5 = Definite	× 10
Hematocrit of < 0.47 in men and < 0.42 in women	Men: 47% observed, Women: 42% observed	× 6
Percentage deviation from standard weight	(ideal - observed) / ideal × 100	× 1

Primary reference: (Best, 1976).

Validations: (Yoshida, 1999; Jorgensen, 2005).

* One point each is added for each set of complications:

- The presence of joint pains (arthralgia) or frank arthritis
- Inflammation of the iris or uveitis
- Presence of mucocutaneous lesions (erythema nodosum, pyoderma gangrenosum, or aphthous ulcers)
- Anal fissures, fistulae, or abscesses
- Other fistulae (external, enterocutaneous, vesicle, vaginal, etc.)
- Fever over 37.8°C during the previous week

Score interpretation:

- CDAI < 150 is a marker of remission of Crohn's disease.
- CDAI > 450 is a marker of severe Crohn's disease.