A) Inclusion criteria

1. Males and females, 18 to 75 years
2. Diagnosis of large duct PSC (intrahepatic and/or extrahepatic), of more than 24 weeks' duration (defined as cholestatic serum liver tests with consistent MRCP or ERCP 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
3. No significant clinical concern for cholangiocarcinoma based on clinical, laboratory or imaging findings in the 12 months preceding Randomization
4. ALP >1.5 × ULN in both Screening and Baseline blood tests (taken at least 5 days apart)
5. Subjects receiving UDCA must receive a stable dose for ≥12 weeks prior to Randomization and must not exceed 23 mg/kg/day during this time
6. Subjects with concomitant IBD:
   a. Subjects with UC must have undergone colonoscopy with biopsy confirming no dysplasia or colorectal cancer within 18 months of Randomization;
   b. Subjects with CD must be in remission as defined by a CDAI <150;
   c. Subjects with UC 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
7. Concomitant medications must be stable for > 12 weeks prior to Randomization
8. Female contraception until 18 weeks post last dose
9. Male contraception until 90 days post last dose

B) Exclusion criteria

1. 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. Competing etiology of liver disease (including, but not limited to, viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, (Ig) G4-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. Small duct PSC in the absence of large duct disease
4. 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 (i.e., transient elastography stiffness values ≥14.4 kPa during the screening period
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 MELD score ≥16
9. Subjects with AST or ALT values > 5 x ULN as determined at Screening and/or Randomization blood tests (taken at least 5 days apart)
10. Subjects who show 'clinically significant changes' (as judged by the investigator) in liver transaminase levels on repeated measure will be excluded
11. Subjects with serum Total Bilirubin values > 3 x ULN at Screening and/or at Randomization (taken at least 5 days apart). Subjects who show evidence of 'clinically significant worsening' (as judged by the investigator) of bilirubin between screening and Randomization will be excluded
12. Subjects with known Gilbert's syndrome or a history of elevations in unconjugated (indirect) bilirubin >ULN
13. Subjects with INR >1.5 which does not correct on vitamin k replacement, in the absence of anticoagulants
14. Subjects with serum creatinine >1.4 mg/dL (123 µmol/L) and/or a platelet count <100 x 10^9/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 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.
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 [TIPS])

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 experiencing or suspected with acute cholangitis in the 90 days prior to Randomization, including cholangitis treated with prophylactic antibiotics

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 of biologics and or hospitalization for colitis within 90 days of Randomization

24. Subjects receiving Biologic treatments such as Anti-TNF and Anti-integrin antibodies for ≤ 24 weeks prior to Randomization, or who are expected to begin such treatment throughout the study

25. Subjects treated with Fenofibrate or other fibrates within 24 weeks of Randomization, or that are expected to be treated with fibrates at any time throughout the trial

26. Subjects that use any prohibited medication as described in section 9.1 (see section C)

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: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and 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 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

C) Concomitant Medication

Prohibited Medications

Drug Class	Requirements
UDCA*	Prohibited at doses that exceed 23 mg/kg/day Unstable doses are prohibited within 12 weeks Washout: 12 weeks
Fenofibrate or other fibrates	Prohibited 24 weeks prior to Randomization
Amoxicillin/clavulanate (Augmentin)	Prohibited 24 weeks prior to Randomization
Biologic treatments (e.g., Anti-TNF, Anti-integrin antibodies)	Prohibited 24 weeks prior to Randomization
Vancomycin as treatment for PSC	Prohibited 24 weeks prior to Randomization
Oral or intravenous antibiotics for treatment of cholangitis	Prohibited 90 days prior to Randomization
OCALIVA (Obeticholic Acid; OCA)	Prohibited 12 weeks prior to Randomization
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)
Oral prednisone > 10 mg per day or equivalent	Prohibited 28 days prior to Randomization
Intravenous prednisone	Prohibited 28 days prior to Randomization
Live vaccines	Prohibited 30 days prior to Randomization
Herbal medications other than standard vitamin supplements	Prohibited 28 days prior to Randomization

* No more than 50% of recruited subjects will be on UDCA treatment

- Antibiotics for treatment of cholangitis are not allowed within 90 days prior to subject Randomization (visit 1). Patients on rotating antibiotics treatment cannot be included into

the study. Amoxicillin/clavulanate (Augmentin) is prohibited for 24 weeks prior to subject Randomization (visit 1) and through to the EoS
NOTE: Antibiotics are permitted, as required, during participation in the trial except to amoxicillin/clavulanate that should not be used unless there are no other treatment options available (this should be discussed with the Medical Monitor in advance of its use in this situation, where possible)

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

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 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 Statins is allowed throughout the study without restrictions
- Systemic or enteral therapy for pruritus (e.g. Cholestyramine, Rifampicin, Naltrexone, Sertraline) is allowed provided that subjects have been on a stable dose for ≥12 weeks prior to subject Randomization (visit 1) and are planned to remain on a stable dose throughout the trial
- Acute short-term symptomatic treatment with 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

D) Study Design