CM-101 improved fibrosis biomarkers in patients with primary sclerosing cholangitis: The SPRING Study

CL Bowlus[1], ST Barclay[2], D Joshi[3], MC Londoño[4], P Mantry[5], R Safadi[6], R Aricha[7], C Cirillo[7], M Frankel[7], J Lawler[7], I Vaknin[7], A Mor[7], D Thorburn[8],

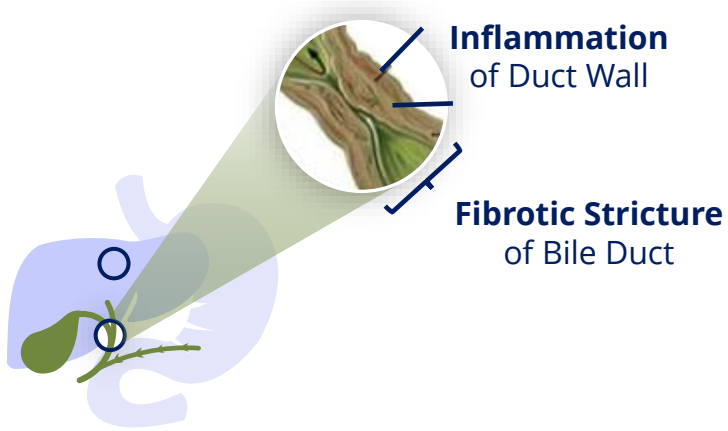
on behalf of the SPRING Study investigators.

[1]University of California, Davis, US [2]Glasglow Royal Infirmary, UK, [3]Institute of Liver Studies Kings College Hospital, UK, [4]Hospital Clinic de Barcelona, Spain, [5]The Liver Institute, Methodist, Dallas, US, [6]Hadassah Hebrew University Hospital, Israel, [7]Chemomab Therapeutics, Ltd, US, [8]Royal Free London NHS Foundation Trust, UK

AASLD 2024: Late Breaking Abstract #5005

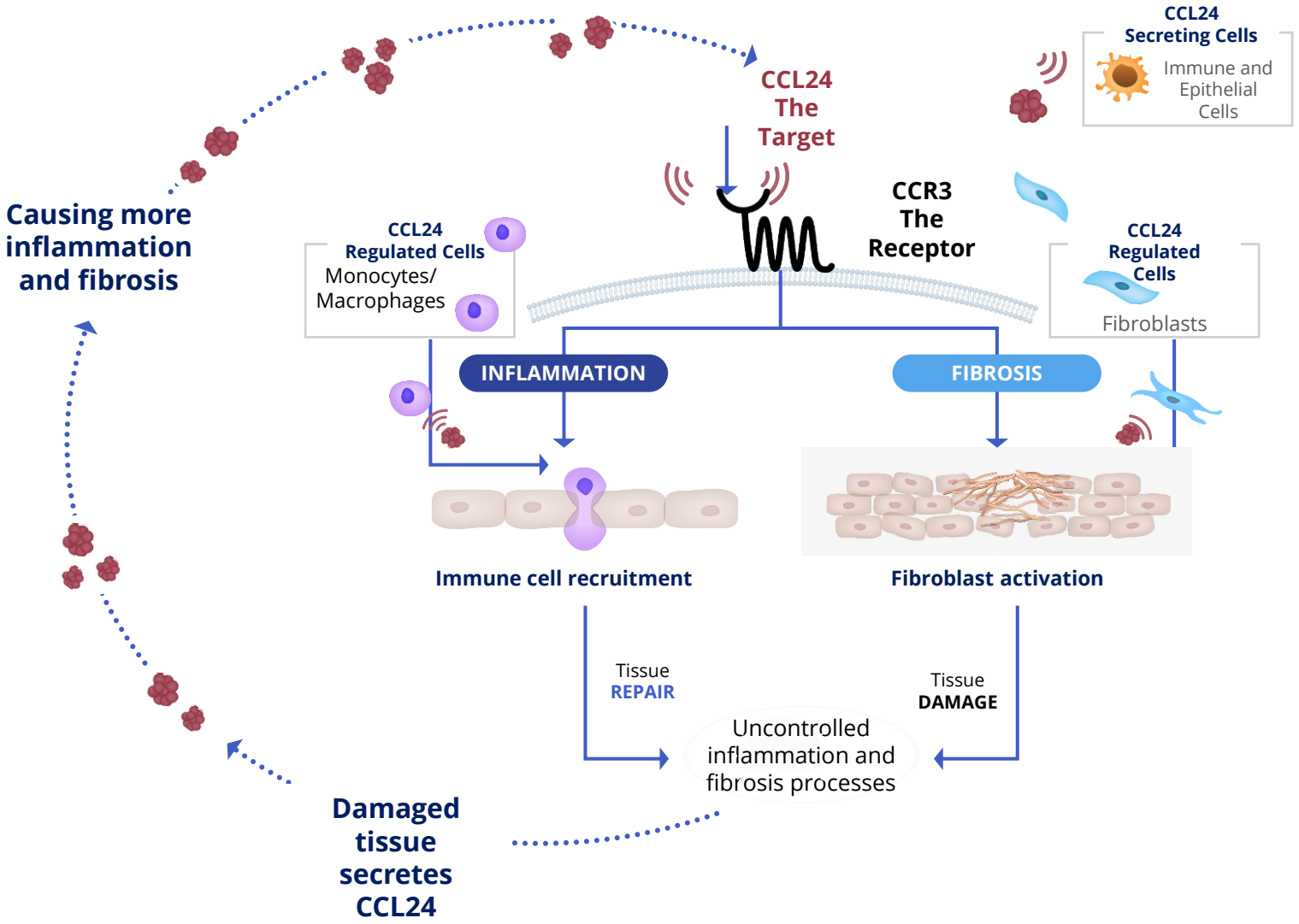
Primary Sclerosing Cholangitis (PSC) is a Rare Cholestatic Liver Disease with High Unmet Needs

- Unknown etiology but associated with inflammatory bowel disease in ~70%
- Characterized by inflammation and fibrotic strictures of the bile ducts
- Complications include those related to cirrhosis as well as acute cholangitis and cholangiocarcinoma
- Median transplant-free survival is ~20 years
- Currently there is no FDA-approved therapy for PSC



(1) Rupp C (2018) United European Gastroenterology Journal. 6(2): 255–262. (2) Palmela C (2018) Gut Liver. 12(1): 17-29. (3) Emek E (2019) Transplantation Proceedings 51(7): 2439-2441. (4) Bakhshi Z (2020). Journal of gastroenterology, 55(5), 523–532. Figure adapted from John Hopkins.

CCL24 (eotaxin-2) is a Chemokine that Promotes Cell Trafficking and Regulates Inflammatory and Fibrotic Activities through the CCR3 Receptor



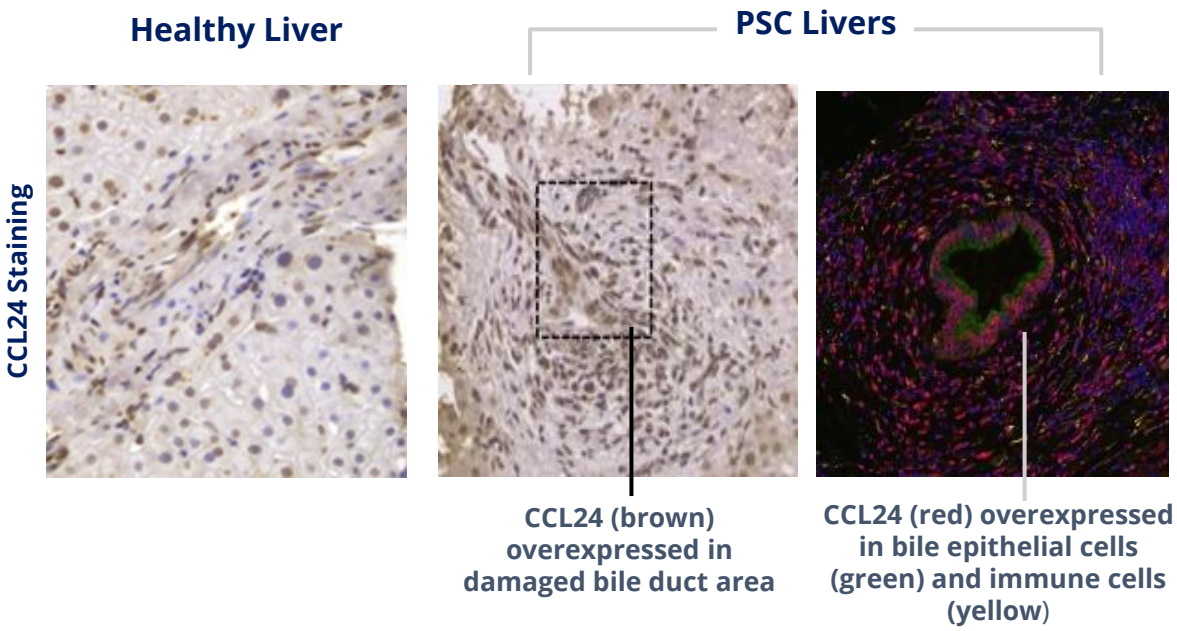
CCL24 – CCR3 promotes inflammation and fibrosis

- Directly activates fibroblasts
- Enhances local monocytes/ macrophages recruitment
- Drives self-reinforcing cycle of inflammation and fibrosis

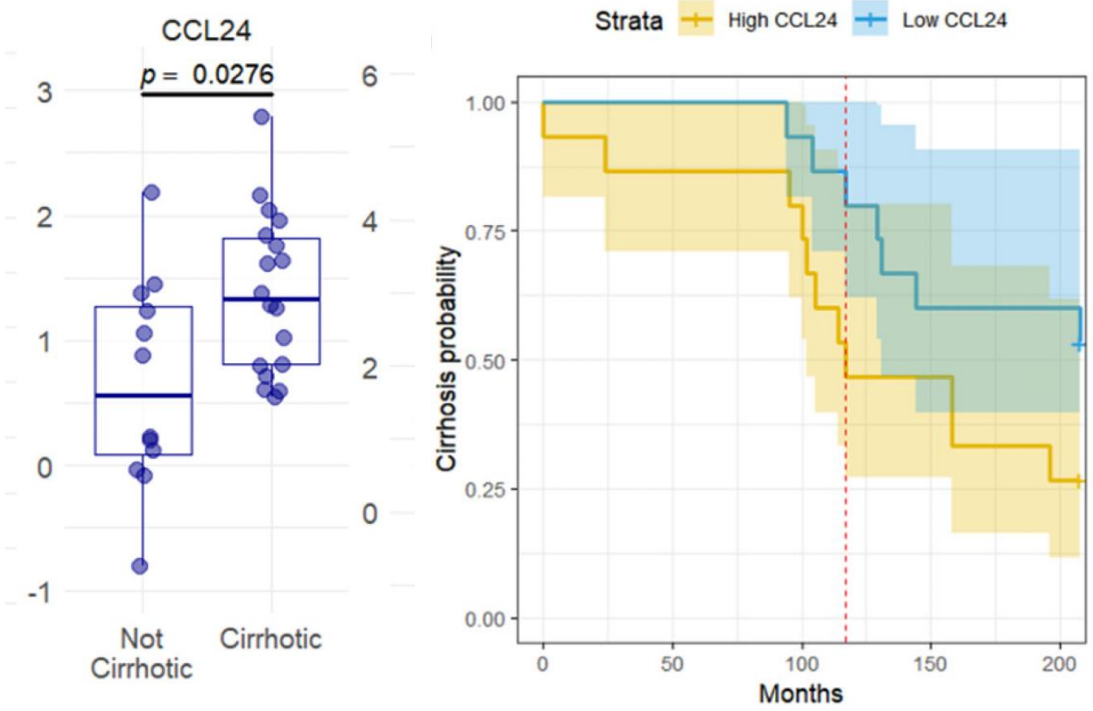
Greenman R, et al, JCI insight 2023

Background: CCL24 Levels are Elevated in PSC Patients and Associated with Cirrhosis

CCL24 levels in liver tissue of healthy subjects vs. patients with PSC



Serum CCL24 level is higher in cirrhosis and associated with risk of progression to cirrhosis



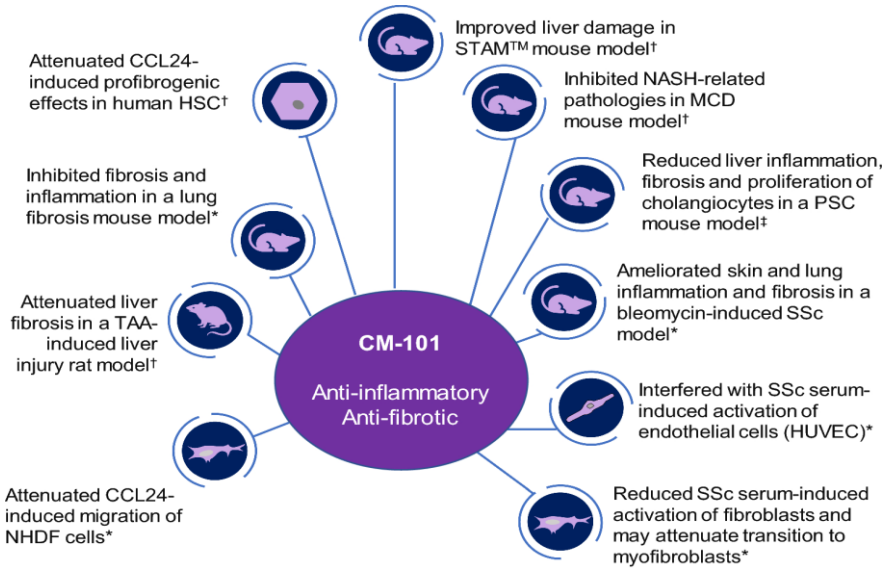
CCL24 expression is significantly and selectively elevated in PSC livers
Elevated serum CCL24 levels in patients are associated with risk of progression to cirrhosis

Greenman et al JCI insight 2023, Snir T, et al. Int J Mol Sci 2024
Low CCL24=levels below median; high CCL24=levels above median; HSC-hepatic stellate cells; NPX-or Normalized Protein eXpression, is a way of measuring how much of a protein is present in a sample

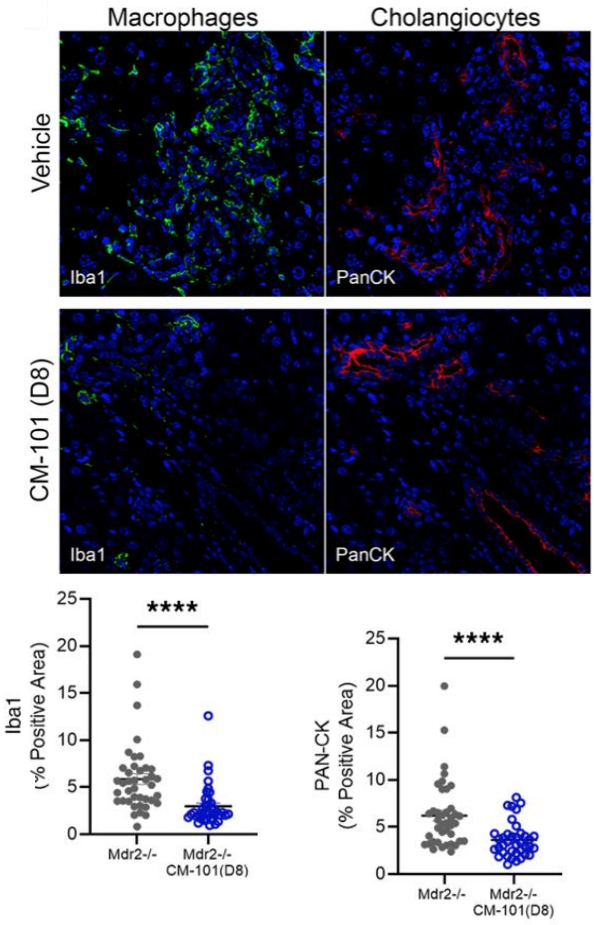
Background: Rationale for Targeting CCL24 with CM-101 in PSC

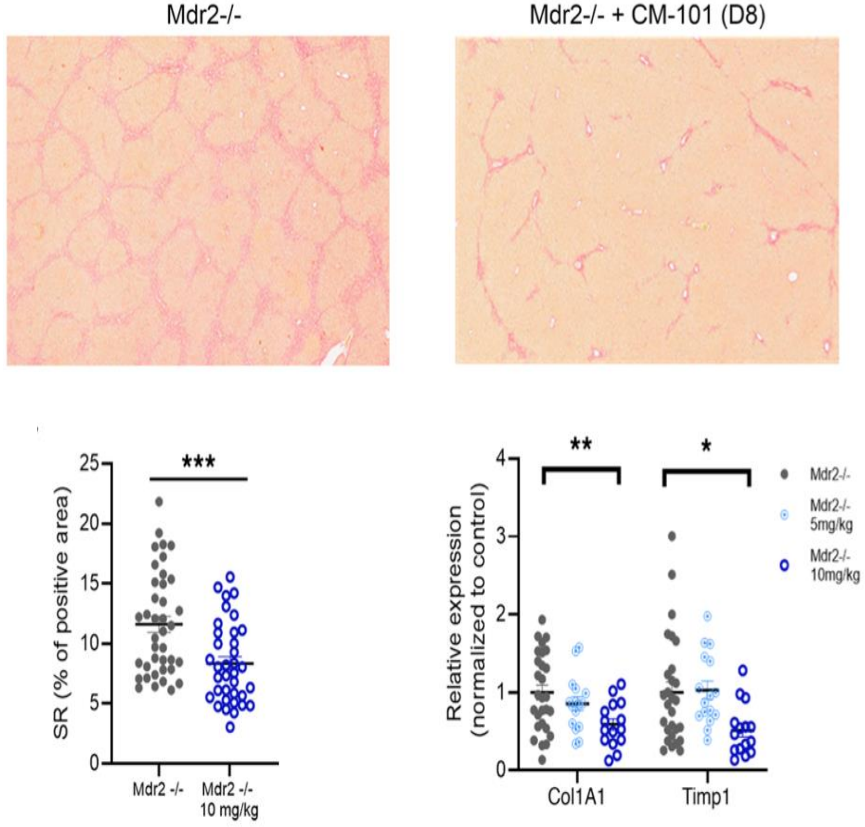
CM-101

- Humanized monoclonal antibody
- Neutralizes CCL24
- Well tolerated in phase 1studies



CM-101 Reduced Liver Injury and Fibrosis in the *Mdr2* $^{-/-}$ Mouse





Reduced Macrophage Recruitment and Biliary Epithelial Cell Proliferation

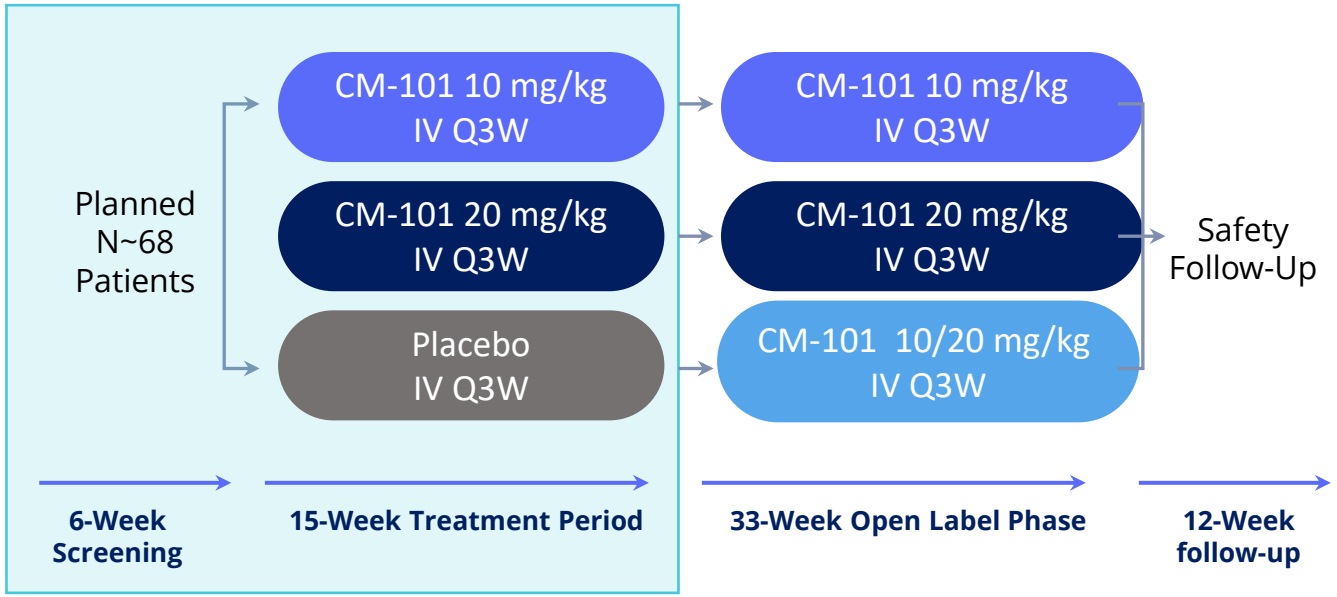
Attenuated Liver Collagen Deposition

A. Mor, et al. Drug Safety 2024; Greenman R, et al. JCI Insight 2023.

Methods: SPRING Study Design

Phase 2, randomized, double-blind, placebo-controlled study of CM-101 in PSC

CM-101 Primary Sclerosing Cholangitis SPRING Study (NCT 04595825)



PSC-primary sclerosing cholangitis; Q3W-once every 3 weeks; IV-intravenous; ALP-alkaline phosphatase; IBD-inflammatory bowel disease; UDCA-ursodeoxycholic acid; VCTE-Vibration controlled transient elastography-measure of liver stiffness; ELF–enhanced liver fibrosis score; Pro-C3-type lll collagen biomarker; AST-aspartate aminotransferase; ALT-alanine aminotransferase, GGT-gamma-glutamyl transferase; ULN –upper limit of normal
*Includes patients with VCTE at baseline >8.7 kPa

Key Enrollment Criteria

PSC patients with large duct disease of >24 weeks duration

- ALP > 1.5 ULN
- Stable IBD allowed
- Stable UDCA treatment allowed

Outcome Measures

Primary – Safety and tolerability
Secondary - Change from baseline to Week 15 in:

- Liver stiffness by VCTE (e.g. FibroScan®)
- ELF score
- Fibrogenesis biomarker (Pro-C3)
- Pruritus
- Liver enzymes (ALP, ALT, AST, GGT) & Total Bilirubin
- Pharmacokinetics
- Pharmacodynamic parameters

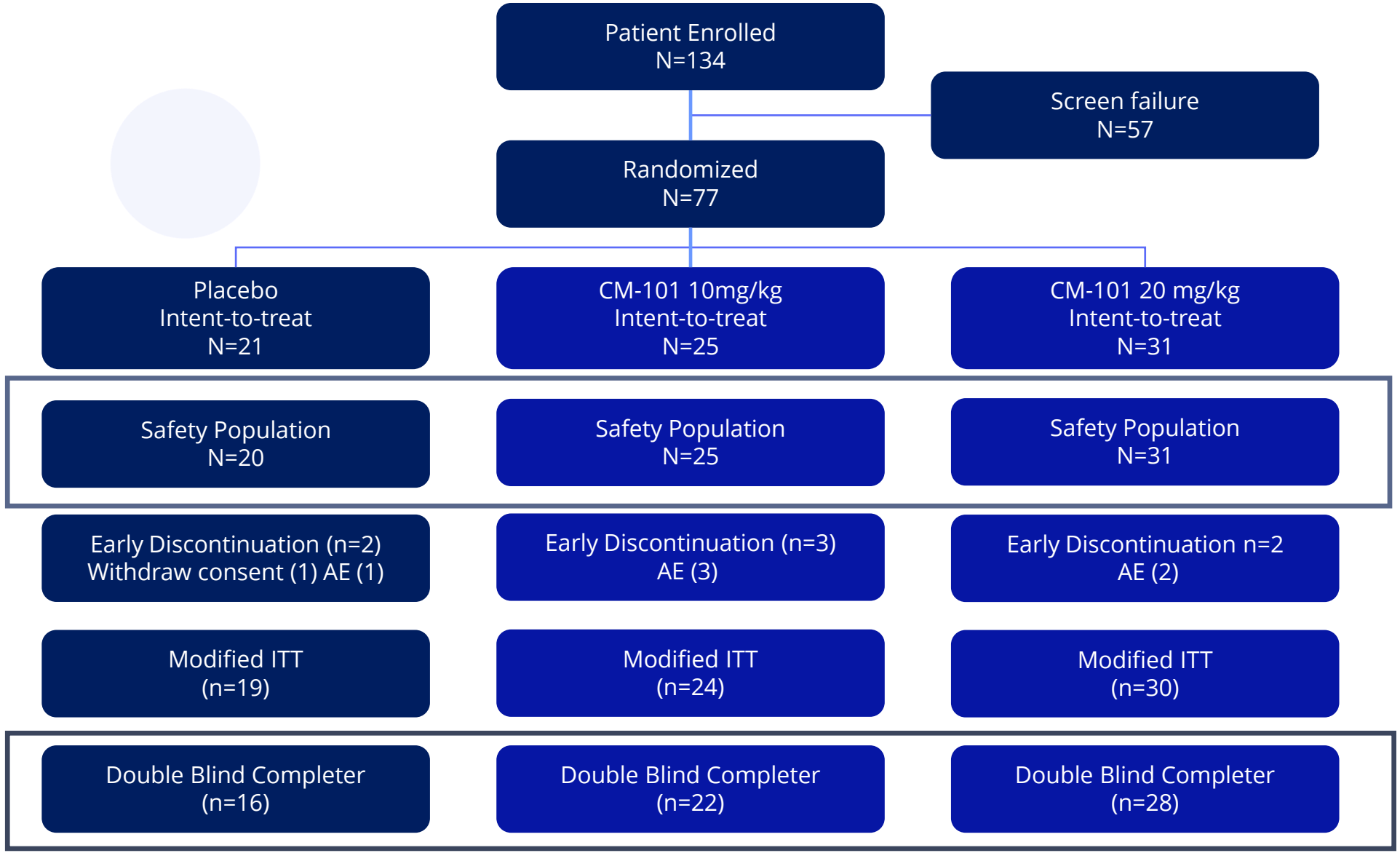
Prespecified Analysis Populations & Subgroup

- All patients
- **VCTE > 8.7kPa**

Territories

- US, UK, Germany, Spain, Israel

Patient Disposition



Safety Population
Randomized and received at least one dose of study treatment

Double Blind Completer
Patients who completed the double-blind period, received all 5 doses of study treatment, and had both a baseline and at least 1 post-dose measurement of ALP and ELF assessments

Results: Patient Demographics and Baseline Characteristics (Safety Population)

Characteristic	Placebo n=20	CM-101 (10 mg/kg) n=25	CM-101 (20 mg/kg) n=31
Age (year), mean, (range)	40.5 (23–75)	48.6 (23–74)	45.6 (23–67)
Male Gender, n, (%)	13 (65%)	16 (64%)	17 (55%)
Race, n, (%) White Black Asian Multiple/ not reported/ unknown	 19 (95%) 1 (5%) 0 (0) 0 (0)	 19 (76%) 1 (4%) 0 (0) 5 (20%)	 28 (90%) 2 (7%) 1 (3%) 0 (0)
Concomitant Ursodeoxycholic acid use, n, (%)	15 (75%)	15 (60%)	18 (58%)
IBD, n (%) Crohn's disease Ulcerative colitis	9 (45%) 3 (33%) 6 (67%)	18 (72%) 3 (17%) 15 (83%)	20 (65%) 5 (25%) 15 (75%)
Alkaline Phosphatase (U/L), Mean (SD)	355 (203)	333 (189)	325 (167)
Alanine Aminotransferase (U/L), Mean (SD)	121 (83)	91 (63)	83 (51)
Aspartate Aminotransferase (U/L), Mean (SD)	87 (54)	59 (27)	64 (31)
Total Bilirubin (mg/dL), Mean (SD)	0.89 (0.5)	0.85 (0.6)	0.98 (0.4)
Serum CCL24 (ng/L), Mean (SD)	947 (594)	1139 (710)	978 (757)
PRO-C3 (ng/mL), Mean (SD)	49.4 (16.5)	57.6 (28.2)	49.6 (22.4)
Enhanced Liver Fibrosis Score (ELF), Mean (SD)	9.75 (1.06)	9.66 (1.03)	9.84 (1.11)
Liver stiffness by VCTE (kPa), Median (range)	9.0 (3-22)	9.7 (3–69)	8.5 (5–74)

Patient demographics and baseline characteristics were similar across cohorts

Results: Safety and Tolerability Profile

Treatment Emergent Adverse Events N, (%)	Placebo n=20	CM-101 10mg/kg n=25	CM-101 20mg/kg n=31	All CM-101 n=56
Treatment Emergent Adverse Events (TEAE)	15 (75%)	18 (72%)	28 (90%)	46 (82%)
Related to study drug	9 (45%)	7 (28%)	16 (52%)	23 (41%)
Serious TEAE	1 (5%)	2 (8%)	0 (0)	2 (4%)
Related to study drug	0	0	0	0
TEAE leading to death	0 (0)	0 (0)	0 (0)	0 (0)
TEAE leading to treatment discontinuation	1 (5%)	3 (12%)	2 (7%)	5 (9%)

Overall TEAEs were mostly mild and distributed similarly across cohorts.
No Serious TEAEs were related to study drug.

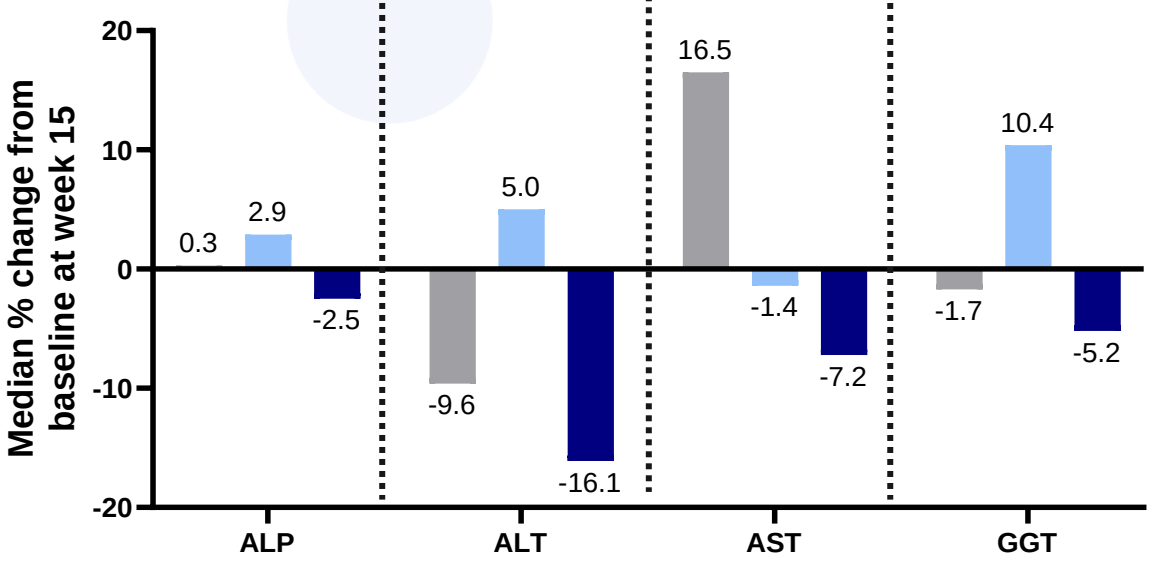
Results: Most Common Treatment Emergent Adverse Events

Treatment Emergent Adverse Events, n (%) ≥10% Frequency	Placebo n=20	CM-101 10mg/kg n=25	CM-101 20mg/kg n=31	CM-101 (All) n=56
Fatigue	6 (30%)	5 (20%)	11 (36%)	16 (29%)
Headache	4 (20%)	2 (8%)	7 (23%)	9 (16%)
Pruritis	2 (10%)	4 (16%)	2 (7%)	6 (11%)
Infusion site pain	3 (15%)	2 (8%)	1 (3%)	3 (5%)
Urinary tract infection	2 (10%)	3 (12%)	1 (3%)	4 (7%)
Diarrhea	2 (10%)	1 (4%)	2 (7%)	3 (5%)
Back pain	2 (10%)	1 (4%)	1 (3%)	2 (4%)
Dizziness	3 (15%)	0 (0)	1 (3%)	1 (2%)
Nausea	2 (10%)	1 (4%)	1 (3%)	2 (4%)
Pyrexia	2 (10%)	0 (0%)	1 (3%)	1 (2%)
Sars-Cov-2 test positive	0 (0%)	3 (12%)	0 (0)	3 (5%)
Abdominal pain	2 (10%)	0 (0%)	0 (0%)	0 (0%)
Crohn’s disease flare/ exacerbation	2 (10%)	0 (0%)	0 (0%)	0 (0%)
Palpitations	2 (10%)	0 (0%)	0 (0%)	0 (0%)

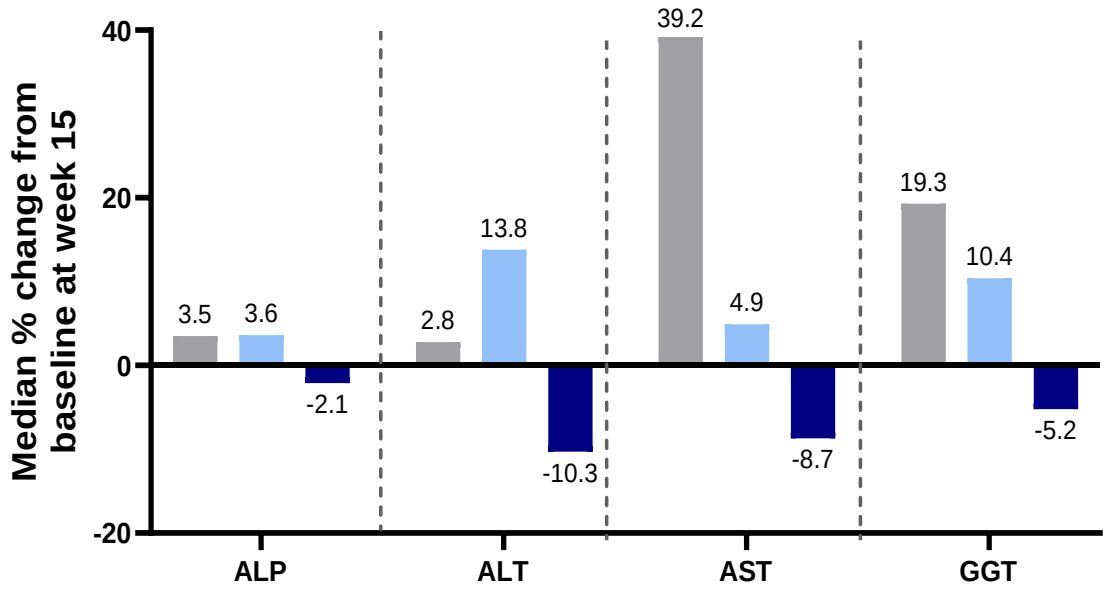
Most adverse events were mild and comparable across placebo and CM-101 cohorts

Results: Liver Biochemistries Tests

All patients



Patients with baseline moderate/advanced disease*



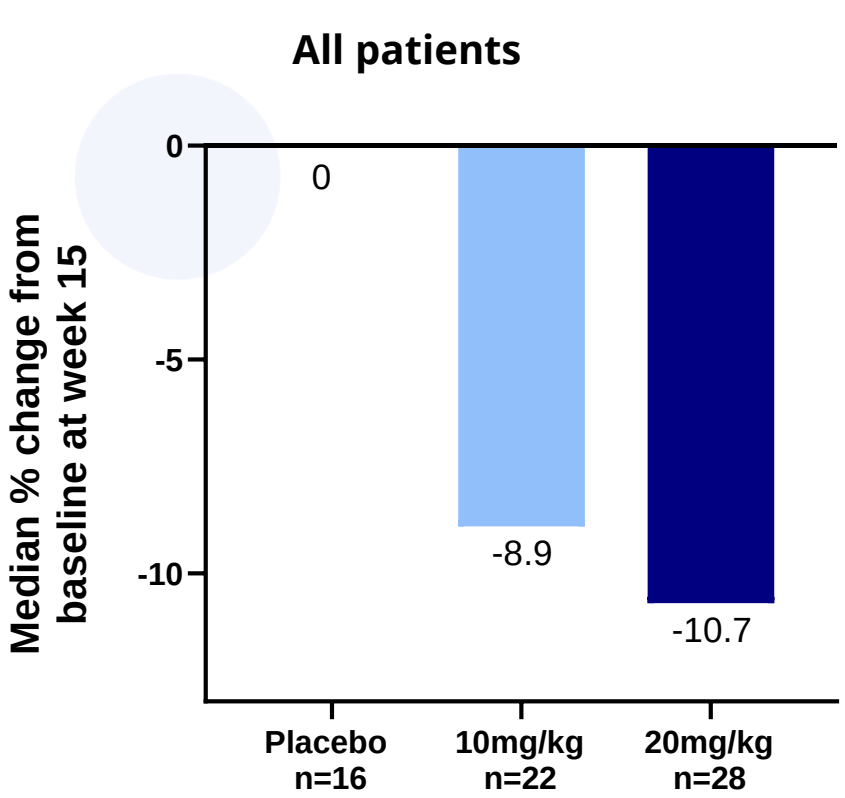
Placebo n=15-16 | 10mg/kg n=18-22 | 20mg/kg n=26-28

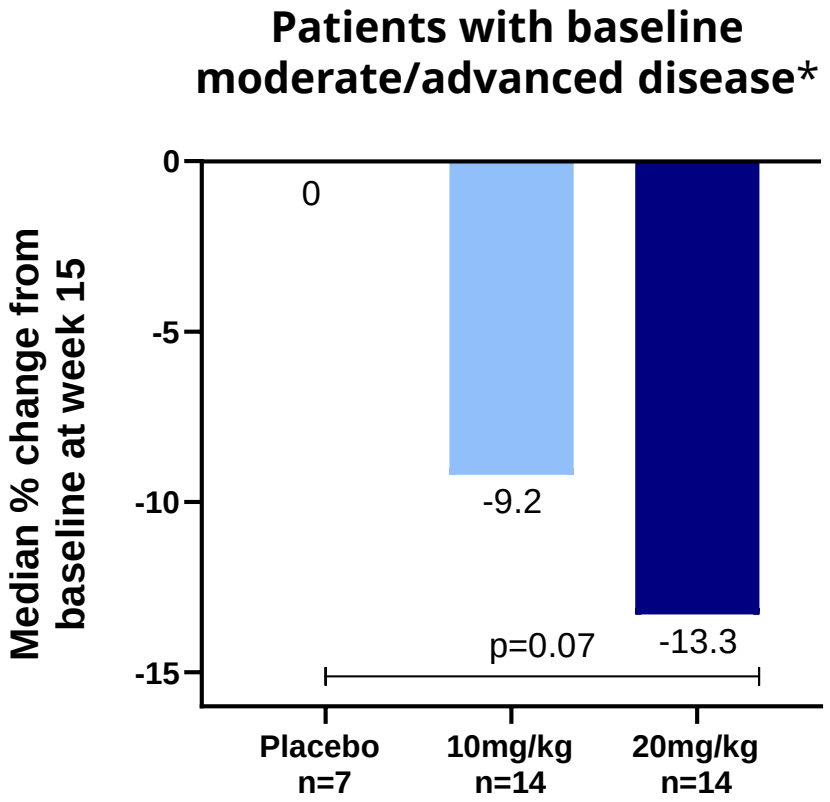
Placebo n=7 | 10mg/kg n=14 | 20mg/kg n=14

Consistent pattern of greatest decline in liver biochemistries seen in CM-101 20 mg/kg treated-patients

*Defined as >8.7 kPa as measured by VCTE (vibration-controlled transient elastography) e.g. FibroScan®

Results: Total Bilirubin

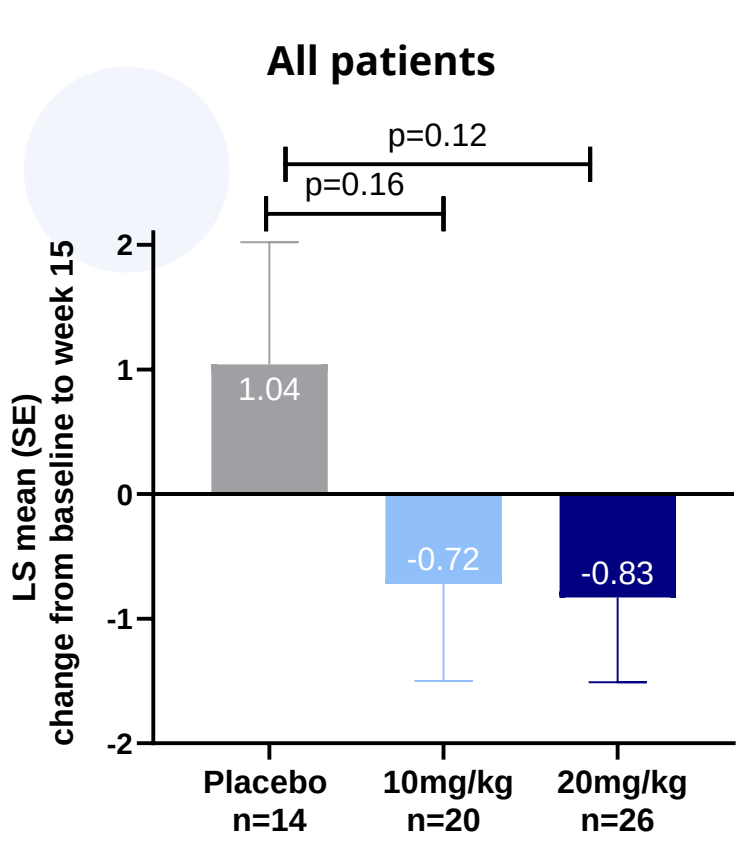


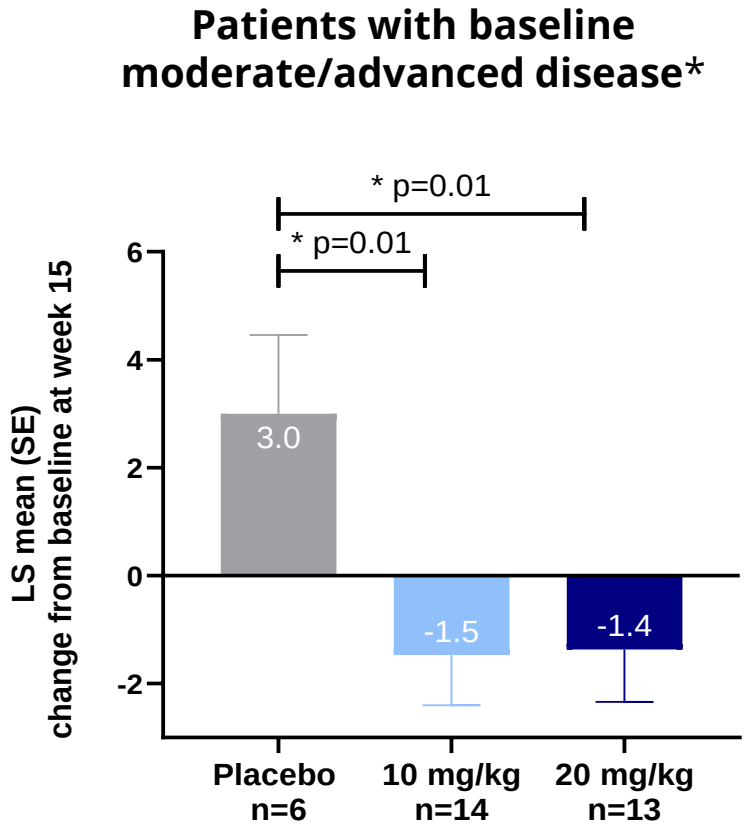


Dose-dependent improvement in bilirubin provides evidence for the anti-cholestatic activity of CM-101

*Defined as >8.7 kPa as measured by VCTE (vibration-controlled transient elastography) e.g. FibroScan®

Results: Liver Stiffness Measurements



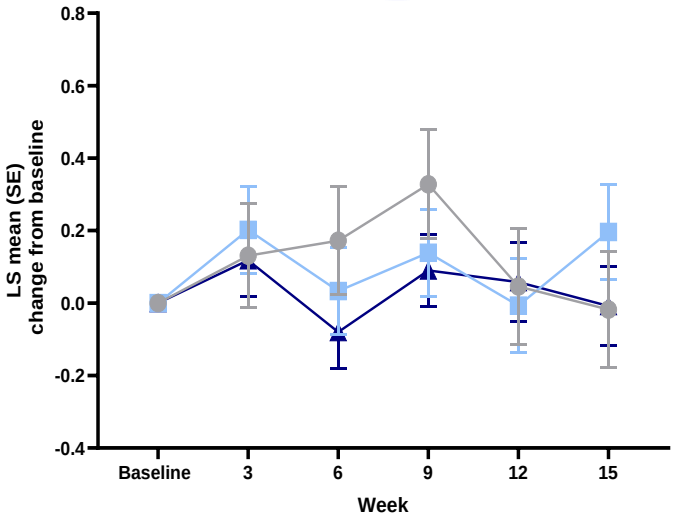


Significantly improved liver stiffness compared to placebo in CM-101-treated patients with moderate/advanced disease

*Defined as >8.7 kPa as measured by VCTE (vibration-controlled transient elastography) e.g. FibroScan®

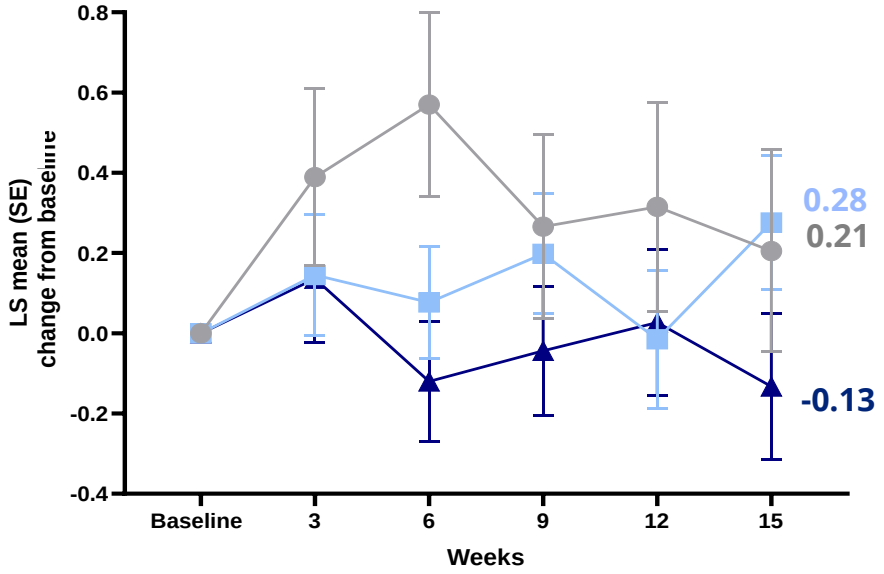
Results: ELF Scores

All patients

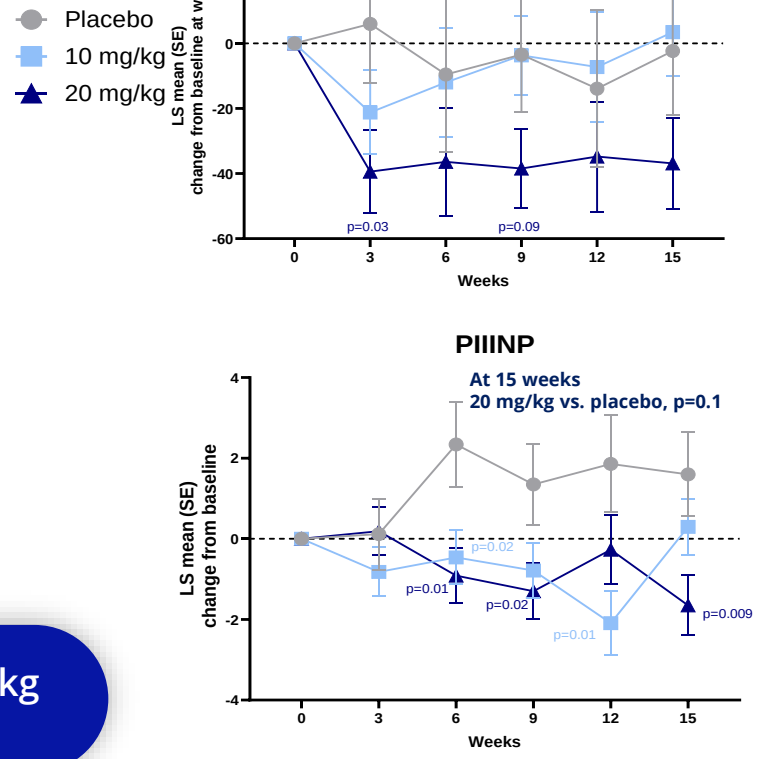


Patients with baseline moderate/advanced disease*

CM-101 20 mg/kg vs. Placebo through 15 weeks
p=0.09



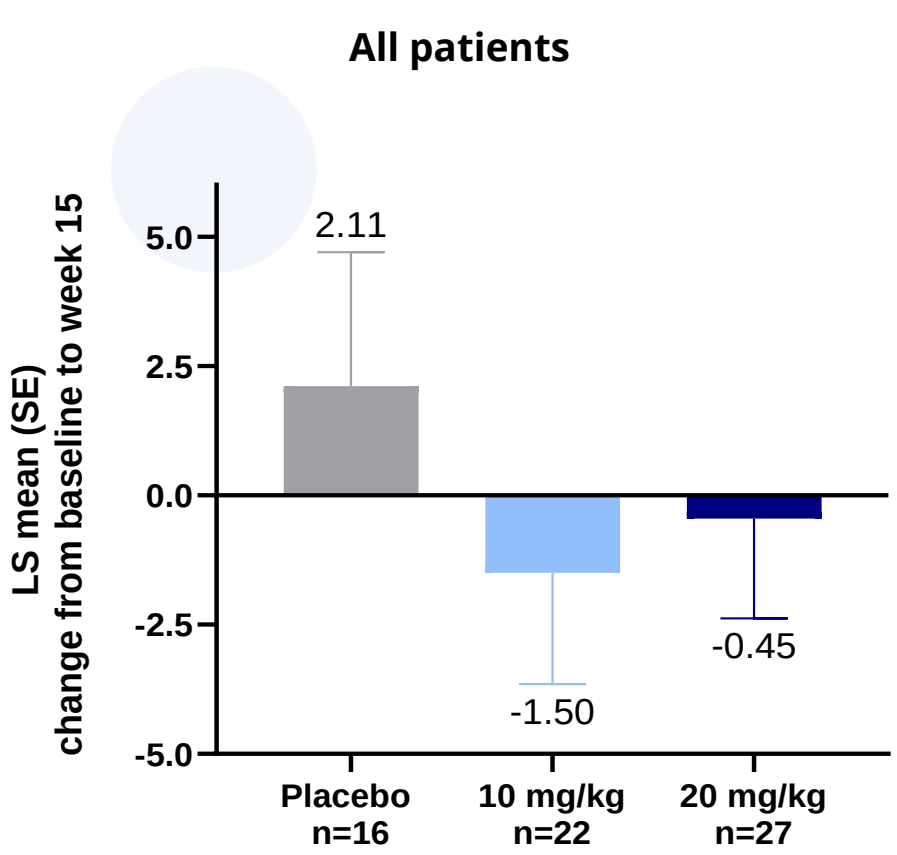
ELF Components-Change from Baseline Over Time

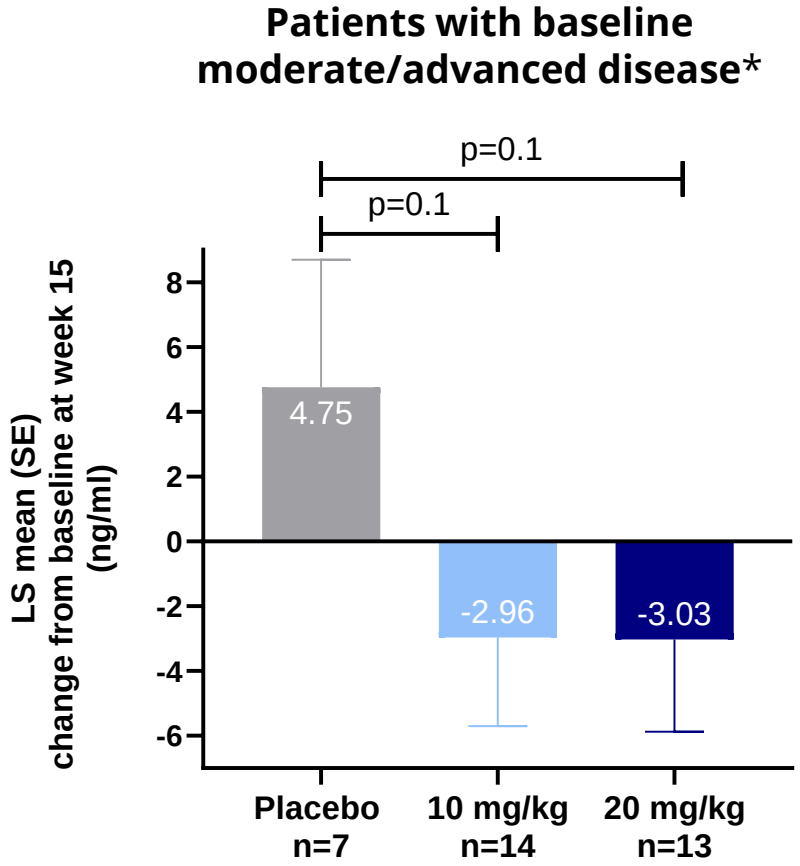


ELF scores were consistently lower in patients with advanced fibrosis treated with 20 mg/kg compared to patients treated with placebo

*Defined as >8.7 kPa as measured by VCTE (vibration-controlled transient elastography) e.g. FibroScan®

Results: PRO-C3



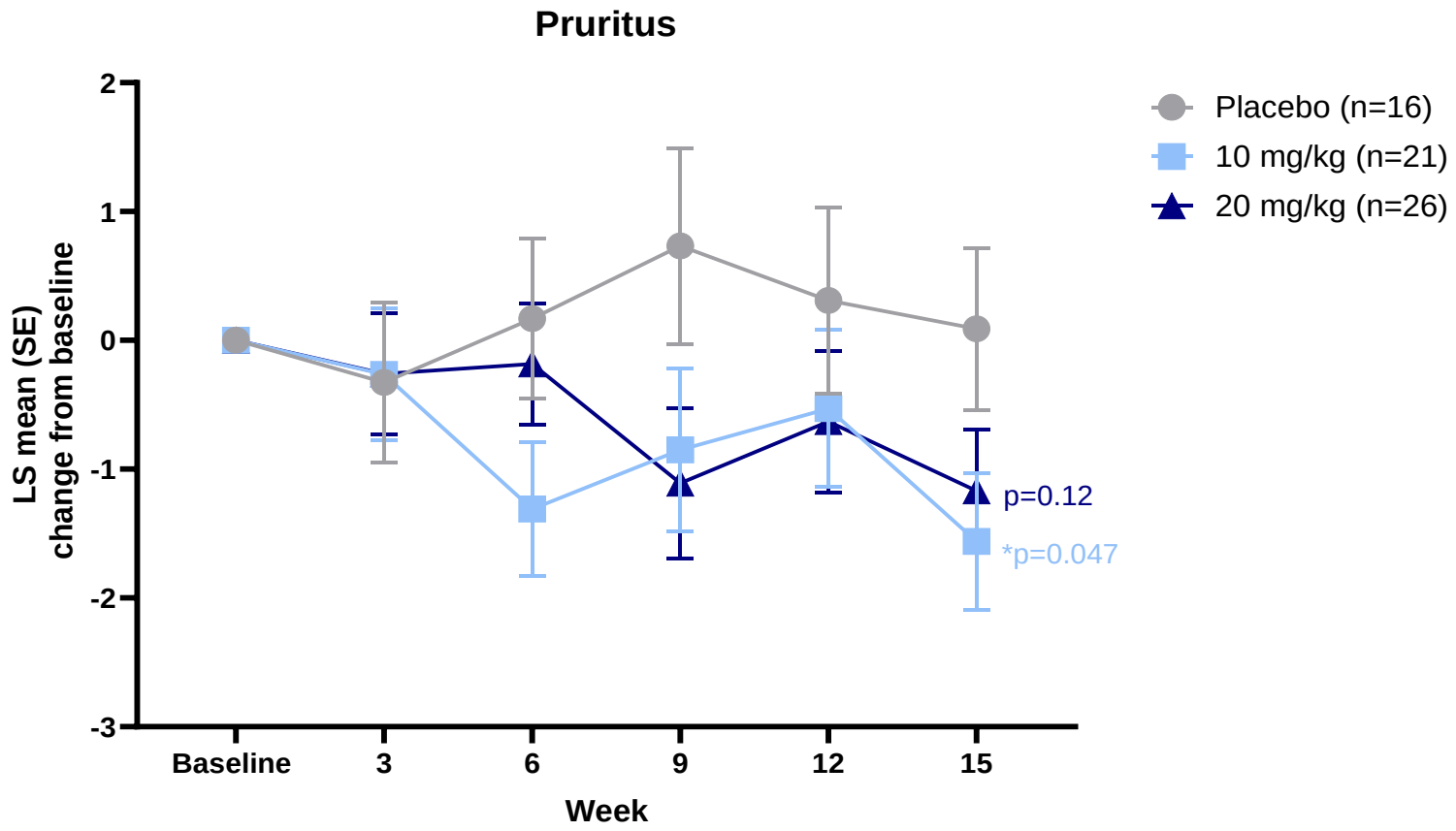


PRO-C3, a serum biomarker of type III collagen synthesis, showed signs of reduction in patients treated with CM-101

PROC-C3: neo-epitope pro-peptide of type III collagen formation.

*Defined as >8.7 kPa as measured by VCTE (vibration-controlled transient elastography) e.g. FibroScan®

Results: 5-D ITCH Total Scores



CM-101-treated patients experienced decreased pruritus scores across all timepoints compared to placebo

*Pruritis assessments based on 5D Itch Score-Total Domain; DBC population

Conclusions and Next Steps

- CM-101 was well tolerated and had a safety profile comparable to placebo
- CM-101 demonstrated dose dependent, anti-inflammatory, anti-fibrotic, and anti-cholestatic effects in patients with PSC
- In a subgroup of patients with moderate to advanced disease, CM-101 showed broad and consistent improvement in biomarkers associated with clinical outcomes
- These findings support further clinical development of CM-101 in patients with PSC

Acknowledgements

- We thank the patients, their families, caregivers, the study investigator and research coordinators who participated in this study
- Enrolling Spring Study Investigators:

Sayed Assem (US)
Justin Boike (US)
Alan Bonder (US)
Christopher Bowlus (US)
Parvez Mantry (US)
Paul Pockros (US)
Daniel Pratt (US)
Ziad Younes (US)

Stephen T Barclay (UK)
Chenchu Ramu-Chimakurthi (UK)
Matthew A Cramp (UK)
Emma M Culver (UK)
Deepak Joshi (UK)
George Mells (UK)
Douglas Thorburn (UK)
Palak Trivedi (UK)

Nimer Assy (Israel)
Gadi Lalazar (Israel)
Yoav Luria (Israel)
Anat Nevo-Shoor (Israel)
Rifaat Safadi (Israel)
Haim Shirim (Israel)
Oren Shibolet (Israel)
Ella Veitsman (Israel)

Udi Zigmond (Israel)
Eli Zuckerman (Israel)
Agustin Albilos-Martinez (Spain)
Marina Berenguer (Spain)
Vanesa Bernal Monterde (Spain)
Maria Carlota Londono (Spain)
Christoph Schramm (Germany)
Kathrin Sprinzl (Germany)

- This study was funded by Chemomab Therapeutics, Ltd.

Thank You