Nebokitug (CM-101), a novel monoclonal antibody targeting CCL24, was safe and well tolerated and showed improvements of biomarkers associated with inflammation, fibrosis, and cholestasis in patients with primary sclerosing cholangitis: The SPRING Study

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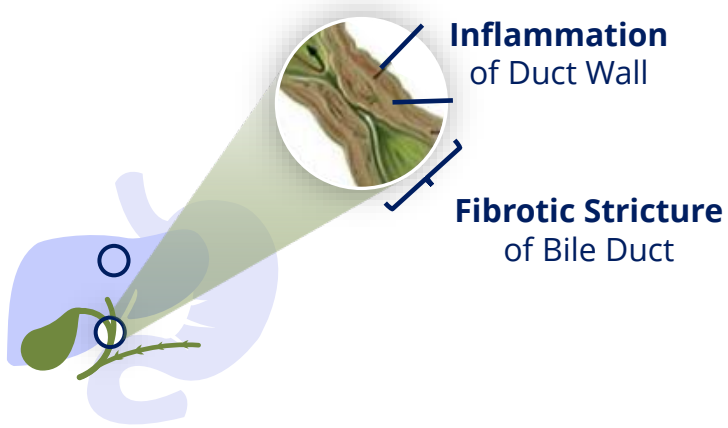
DDW 2025 Abstract # 4250577

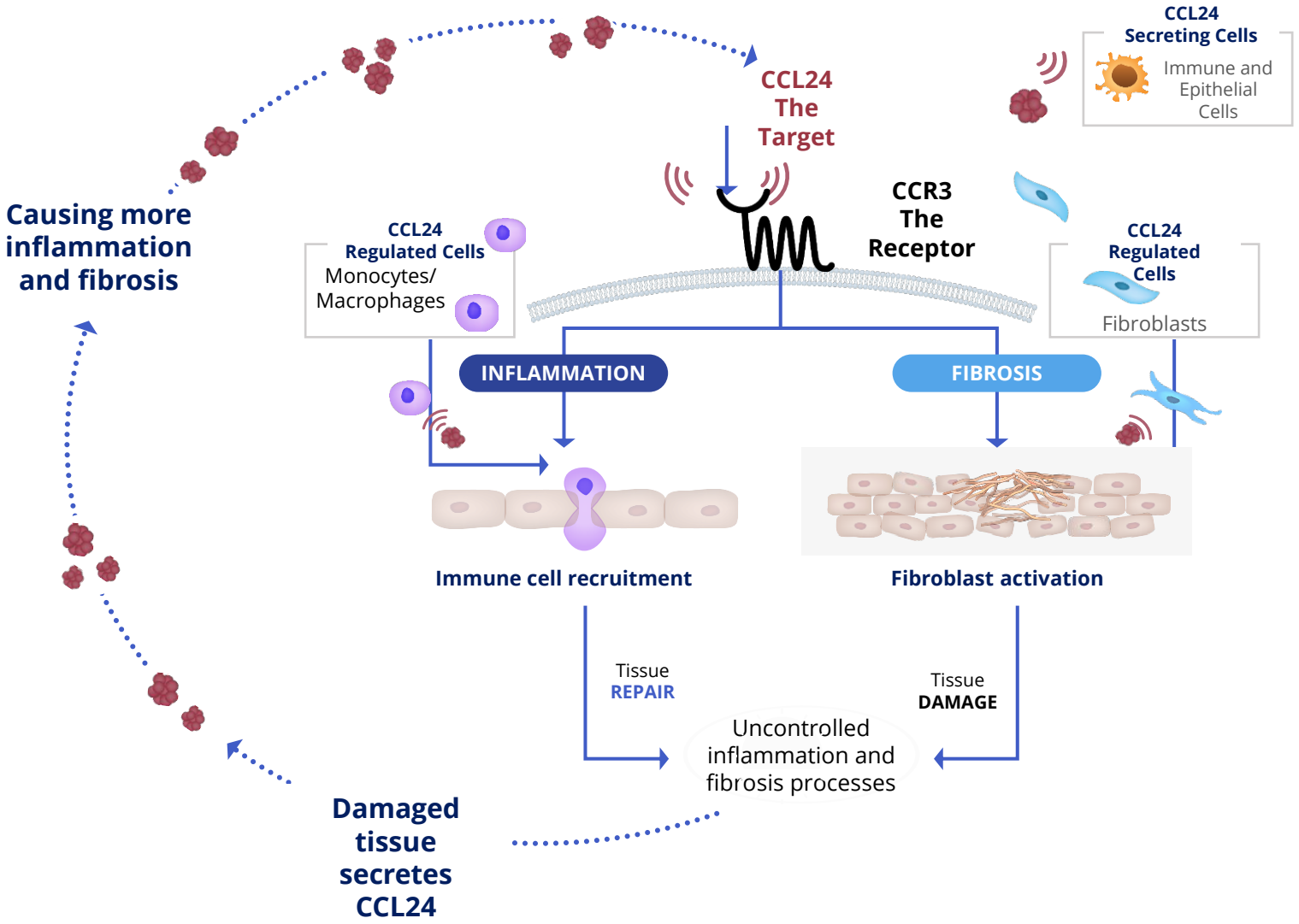
Primary Sclerosing Cholangitis (PSC) is a Rare Cholestatic Liver Disease with High Unmet Needs

- Unknown etiology but associated with inflammatory bowel disease in ~70%
- Characterized by inflammation and fibrotic strictures of the bile ducts
- Complications include cirrhosis, cholangitis, and cholangiocarcinoma
- Median transplant-free survival is ~20 years
- Confers high risk for colon cancer in patients with IBD
- 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 is a Chemokine that Promotes Cell Trafficking and Regulates Inflammatory and Fibrotic Activities through the CCR3 Receptor



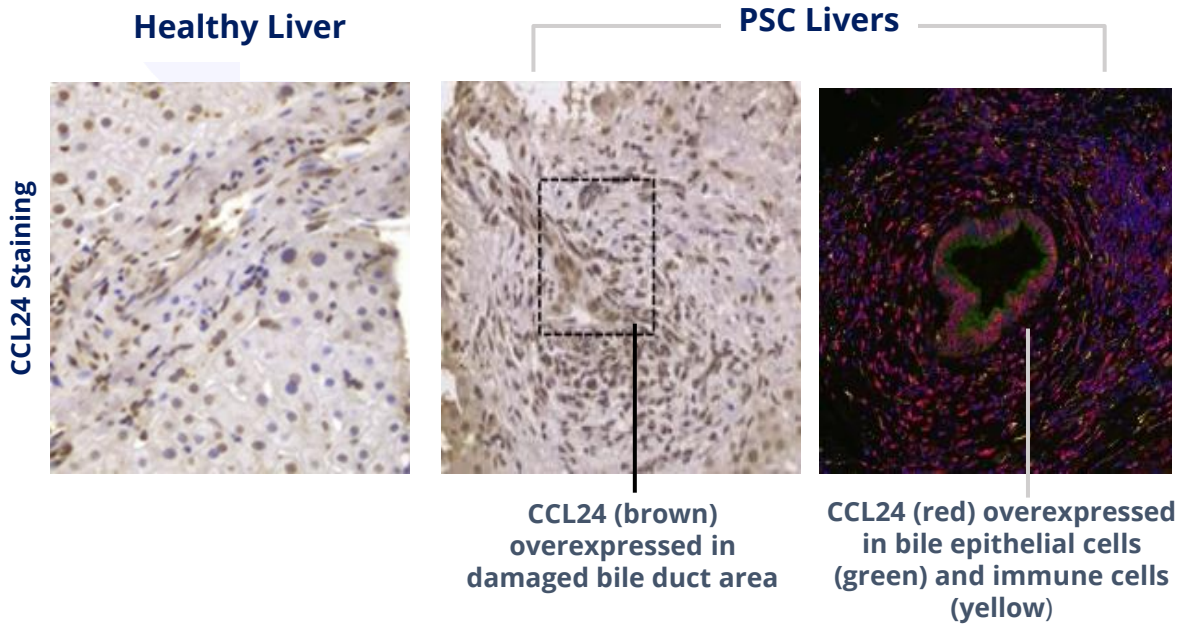
CCL24 – CCR3 promotes inflammation and fibrosis

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

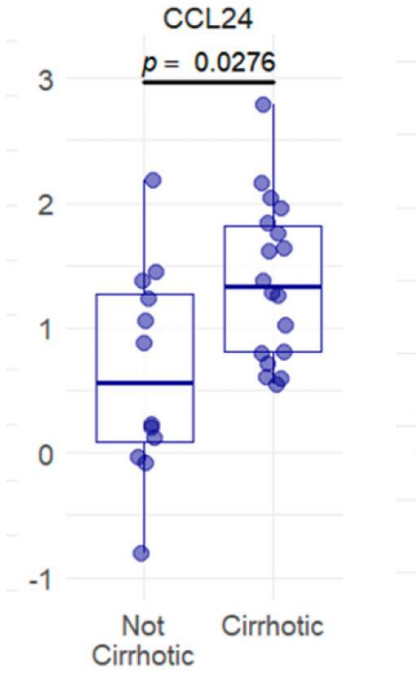
Greenman R, et al, JCI insight 2023

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

CCL24 levels in liver tissue of healthy subjects vs. patients with PSC[1]



Serum CCL24 level was higher in patients with cirrhosis[2]



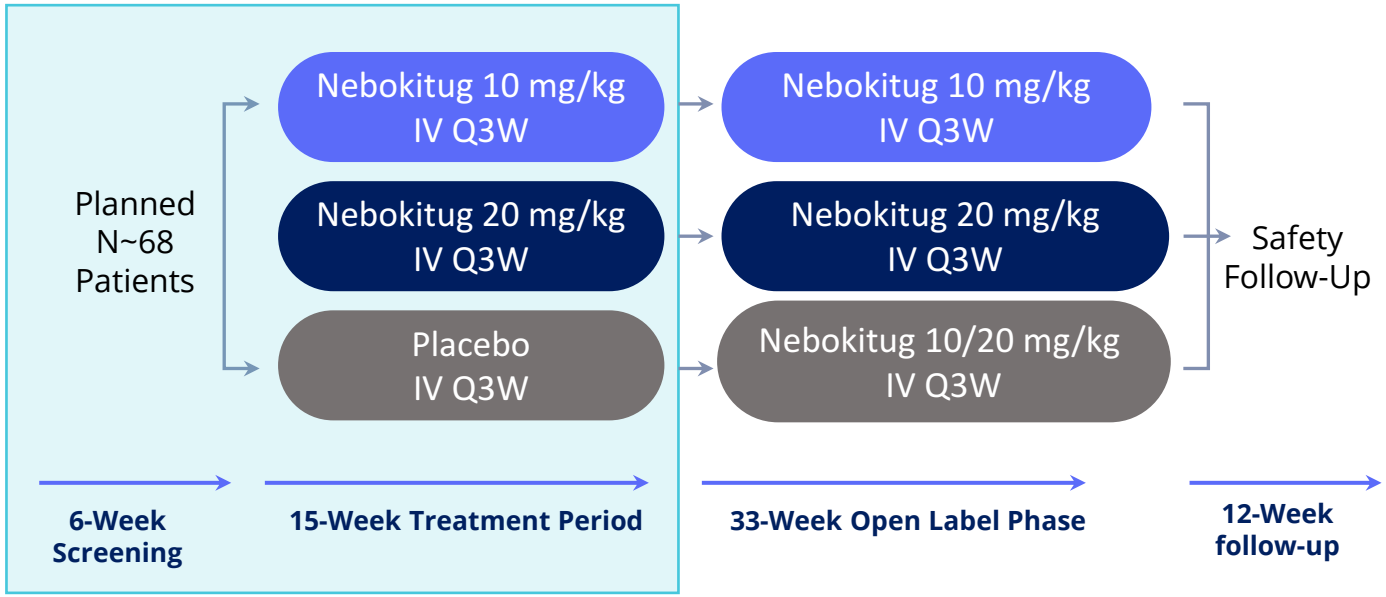
CCL24 expression is significantly and selectively elevated in PSC livers
Elevated serum CCL24 levels was higher in patients with cirrhosis

[1]Greenman et al JCI insight 2023, [2]Snir T, et al. Int J Mol Sci 2024
Low CCL24=levels below median; high CCL24=levels above median

Methods: SPRING Study Design

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

SPRING Study (NCT 04595825)



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**

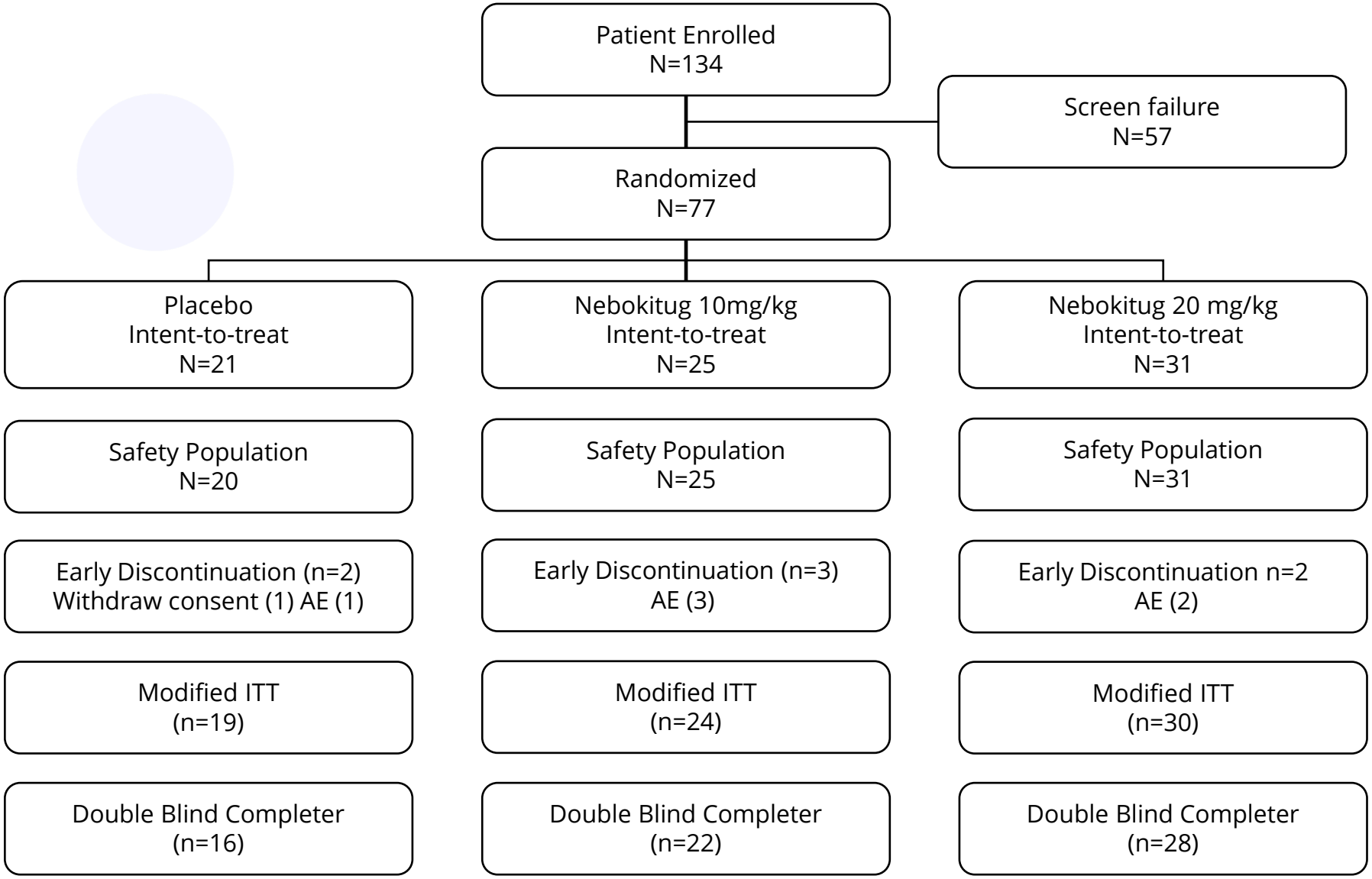
Territories

- US, UK, Germany, Spain, Israel

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

Patient Disposition



Results: Patient Demographics and Baseline Characteristics (Safety Population)

Characteristic	Placebo n=20	Nebokitug (10 mg/kg) n=25	Nebokitug (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	Nebokitug 10mg/kg n=25	Nebokitug 20mg/kg n=31	Nebokitug All 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%)	2 (8%)	2 (7%)	4 (7%)

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

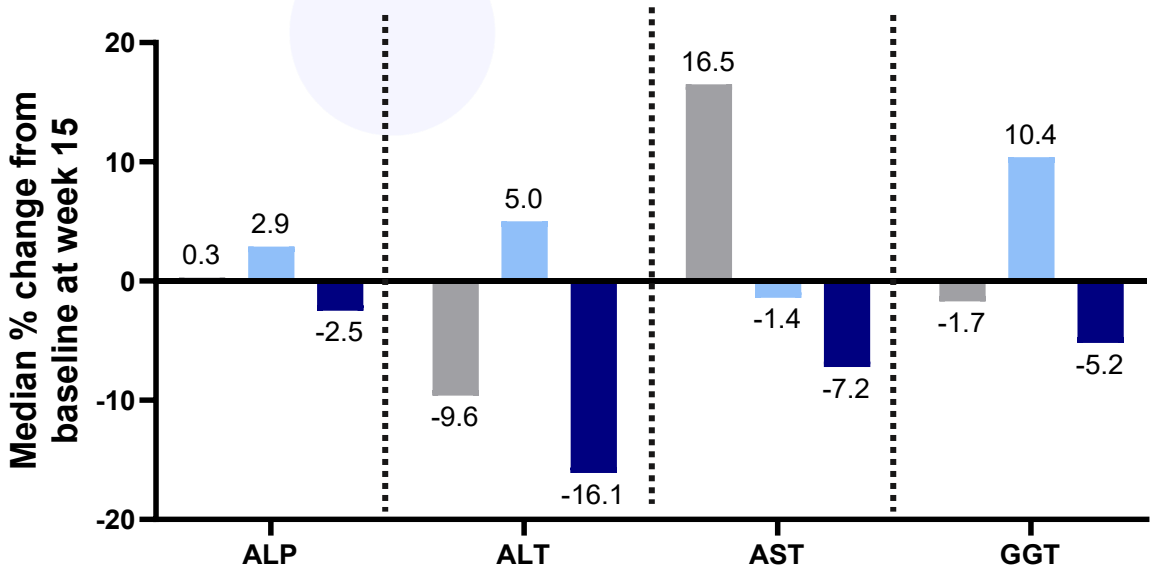
Results: Most Common Treatment Emergent Adverse Events

Treatment Emergent Adverse Events, n (%) ≥10% Frequency	Placebo n=20	Nebokitug 10mg/kg n=25	Nebokitug 20mg/kg n=31	Nebokitug 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%)

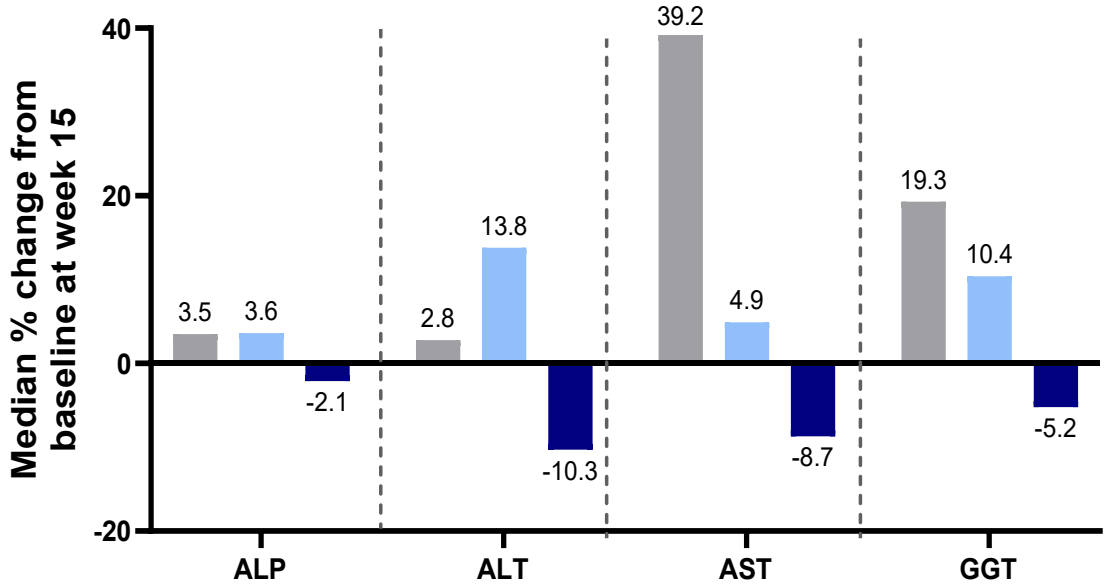
Most adverse events were mild and comparable across placebo and Nebokitug cohorts

Results: Liver Blood Tests

All patients



Patients with baseline moderate/advanced disease*



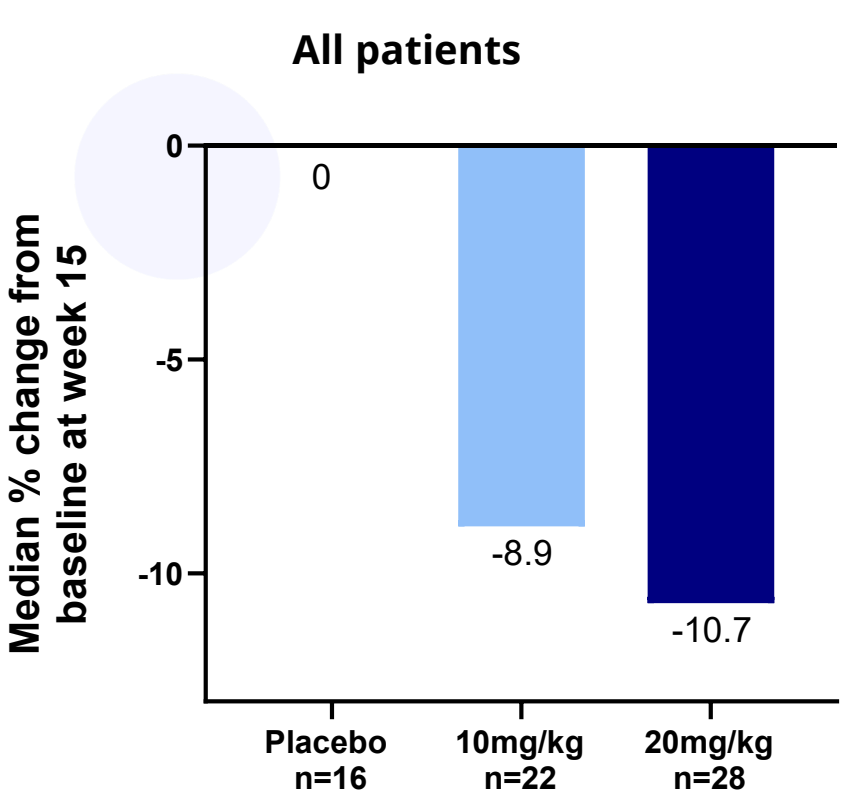
Placebo n=15-16 | 10mg/kg n=18-22 | 20mg/kg n=26-28

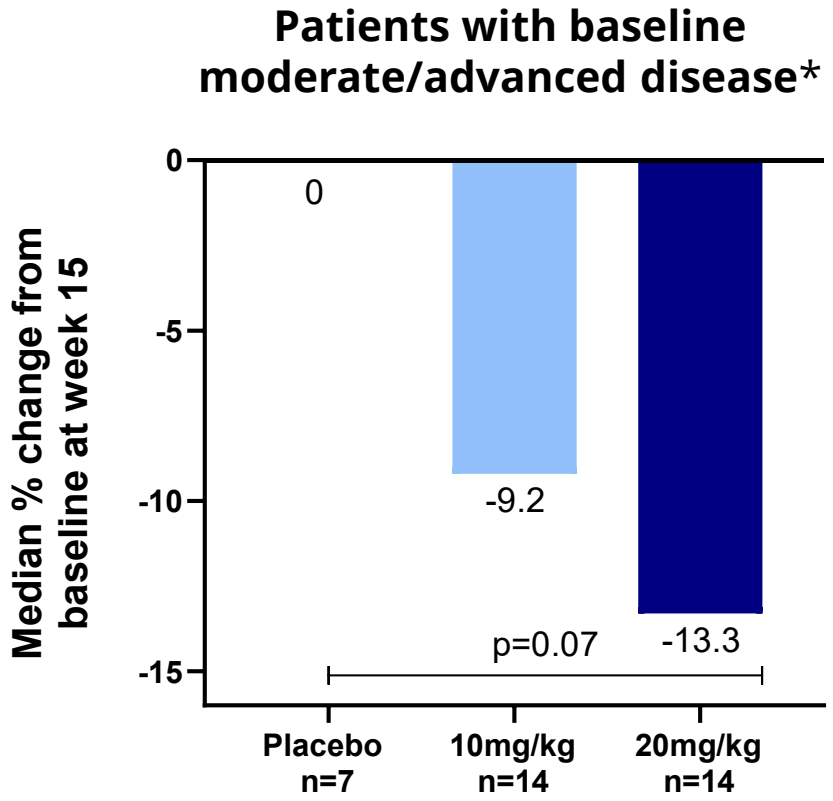
Placebo n=7 | 10mg/kg n=14 | 20mg/kg n=14

Consistent pattern of greatest decline in liver blood tests seen in Nebokitug 20 mg/kg treated-patients

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

Results: Total Bilirubin



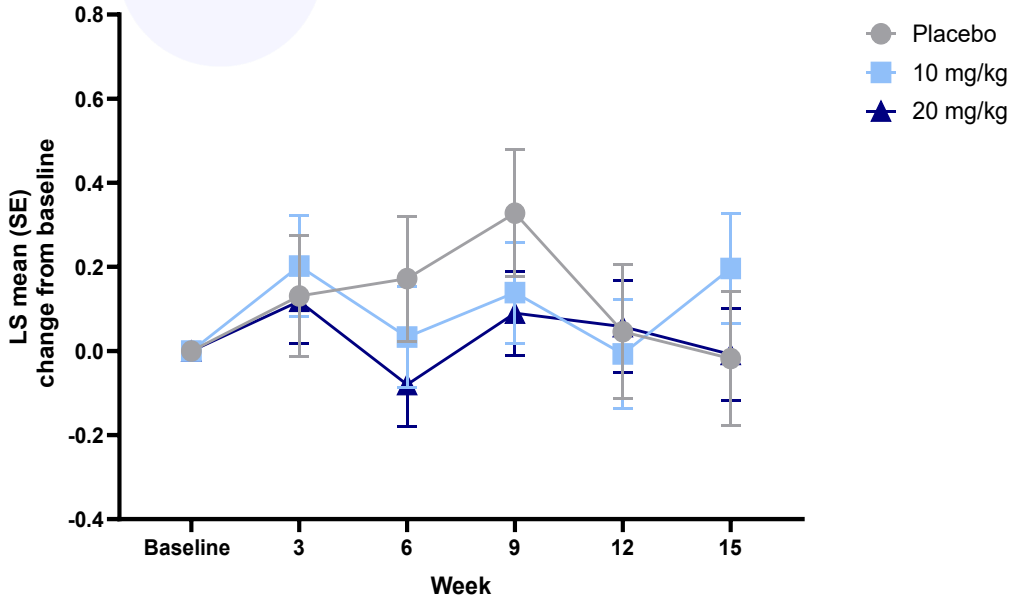


Dose-dependent improvement in bilirubin provides evidence for the potential anti-cholestatic activity of nebokitug

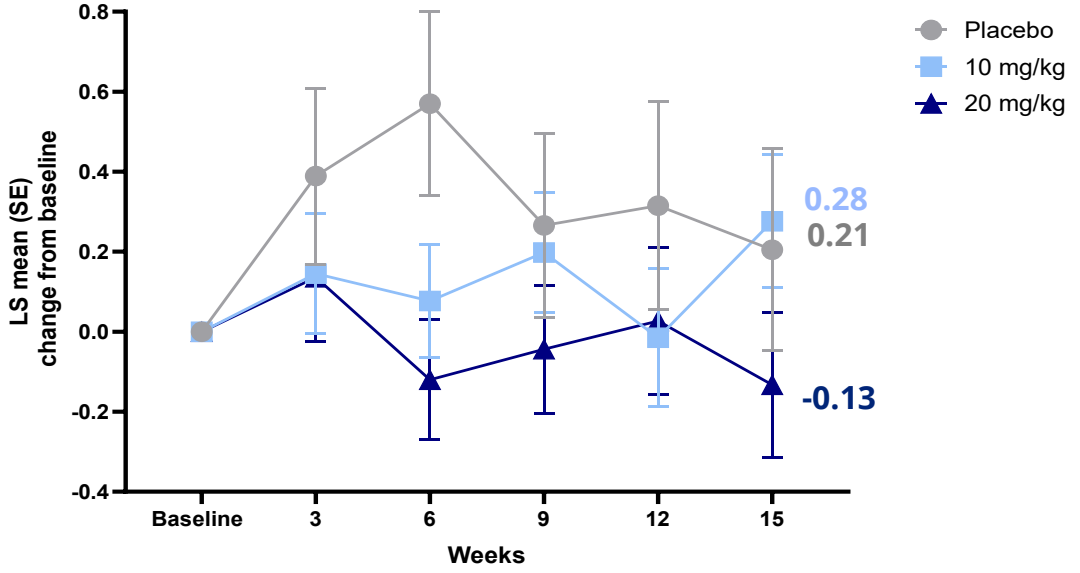
*Defined as >8.7 kPa as measured by VCTE (vibration-controlled transient elastography) e.g. FibroScan®

Results: ELF Scores

All patients



Patients with baseline moderate/advanced disease*

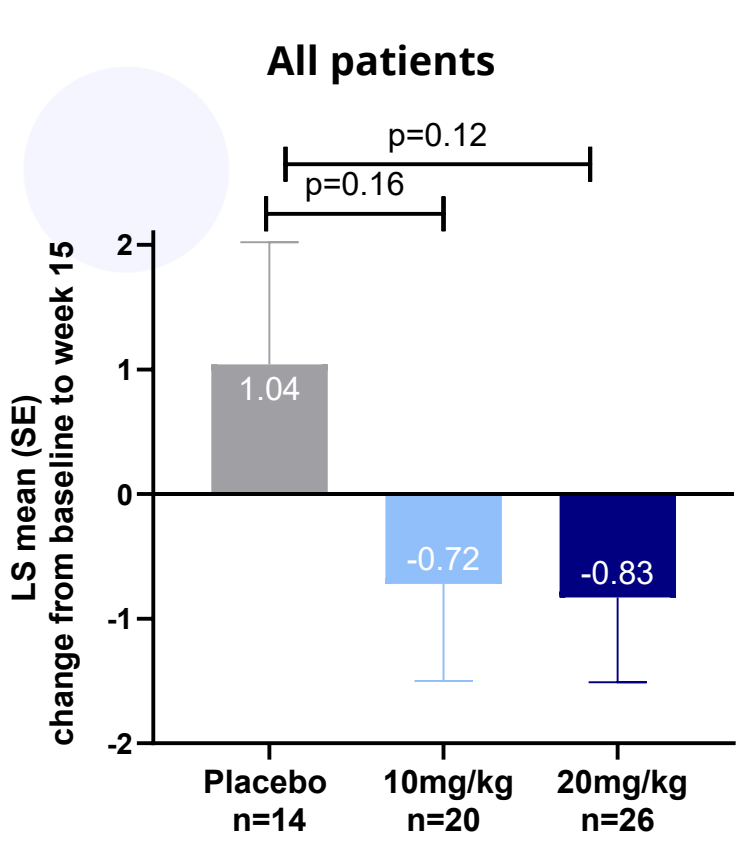


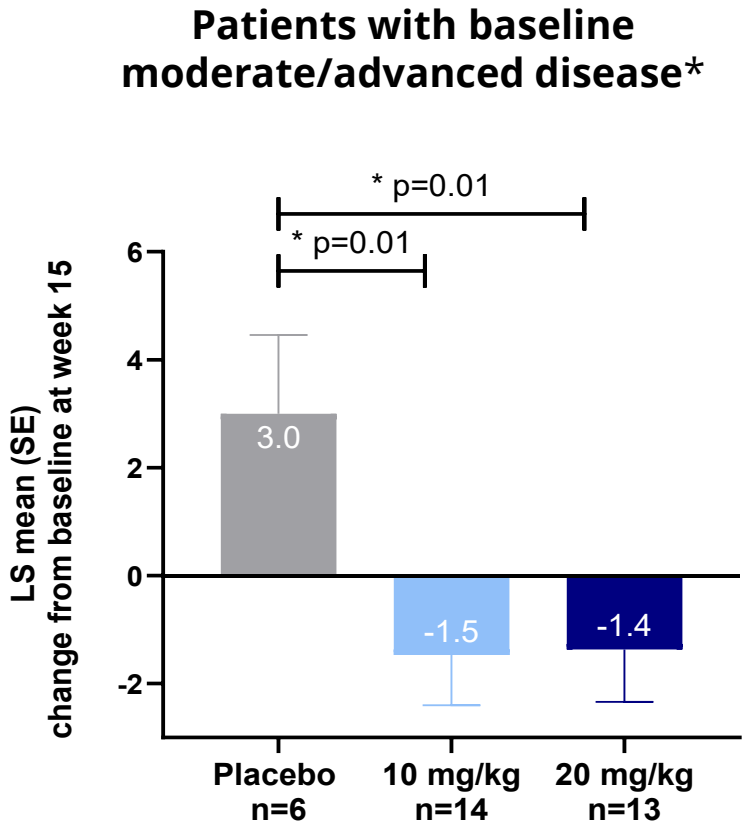
CM-101 20 mg/kg vs. Placebo through 15 weeks p=0.09

ELF scores were consistently lower in patients with advanced fibrosis treated with nebokitug 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: Liver Stiffness Measurements

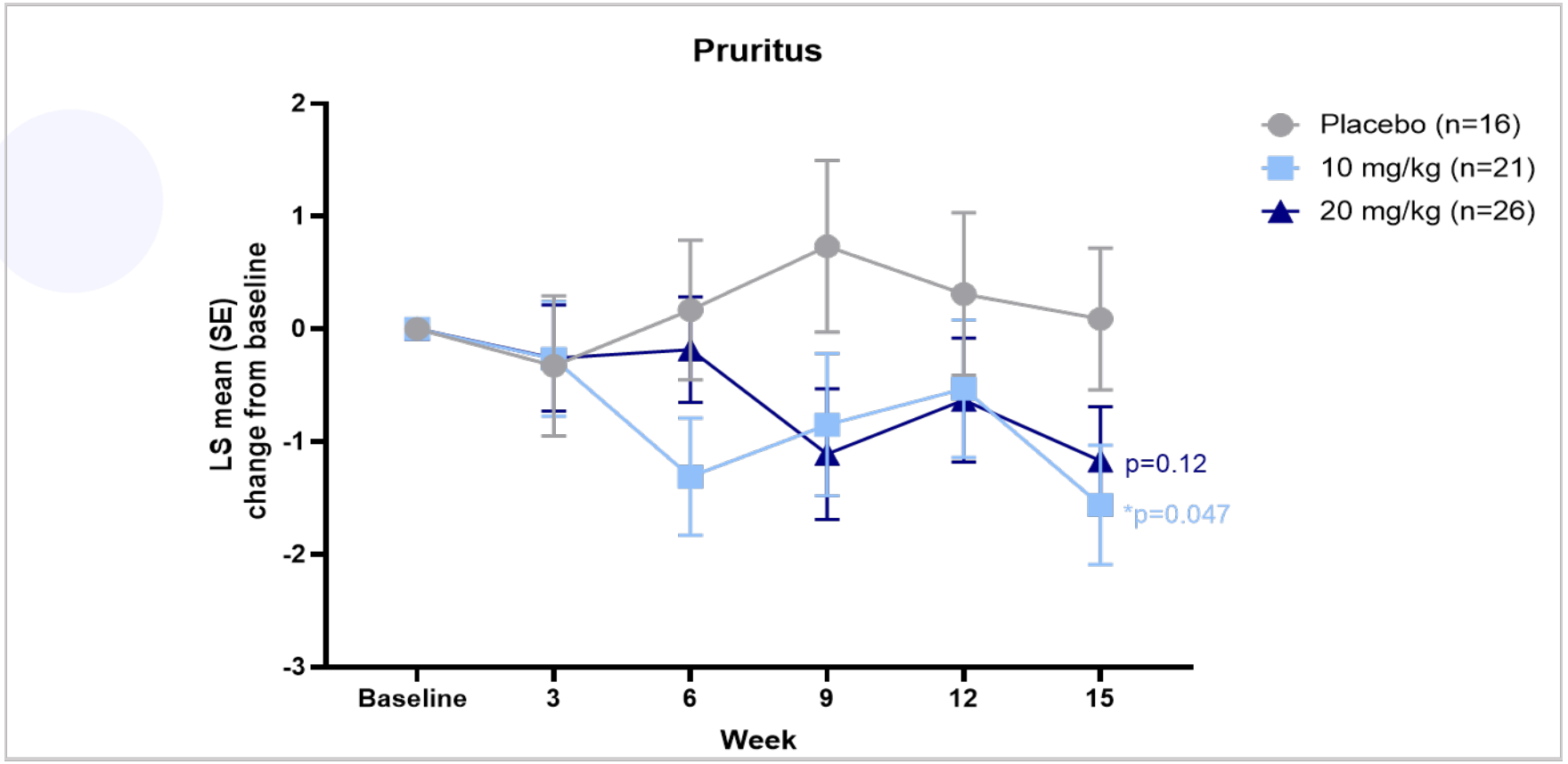




Significantly improved liver stiffness compared to placebo in nebokitug-treated patients with moderate/advanced disease

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

Results: 5-D ITCH Total Scores



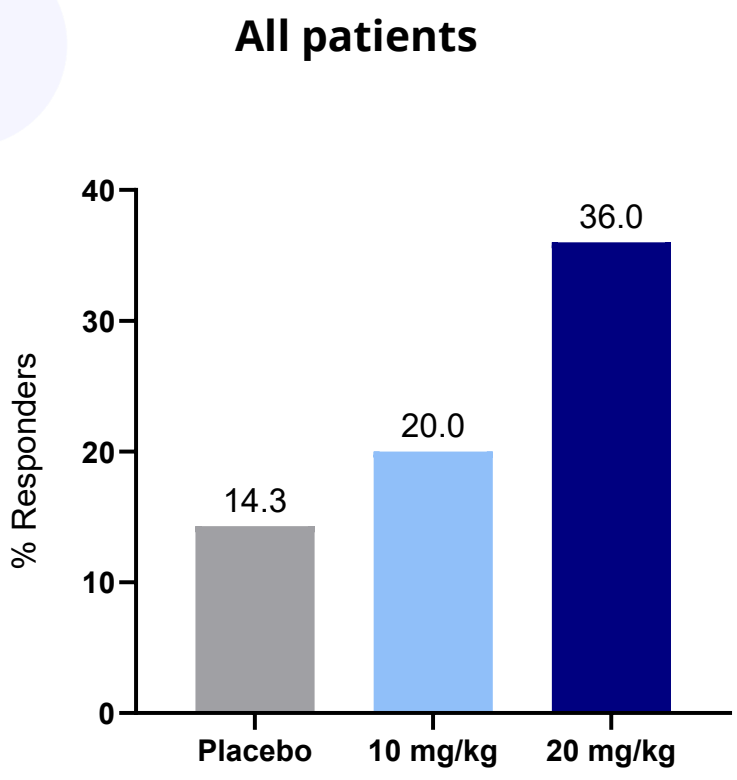
Pruritus at Baseline	Placebo	10 mg/kg	20 mg/kg
Mean (SE)	10.8 (4.4)	10.5 (5.1)	7.9 (2.8)

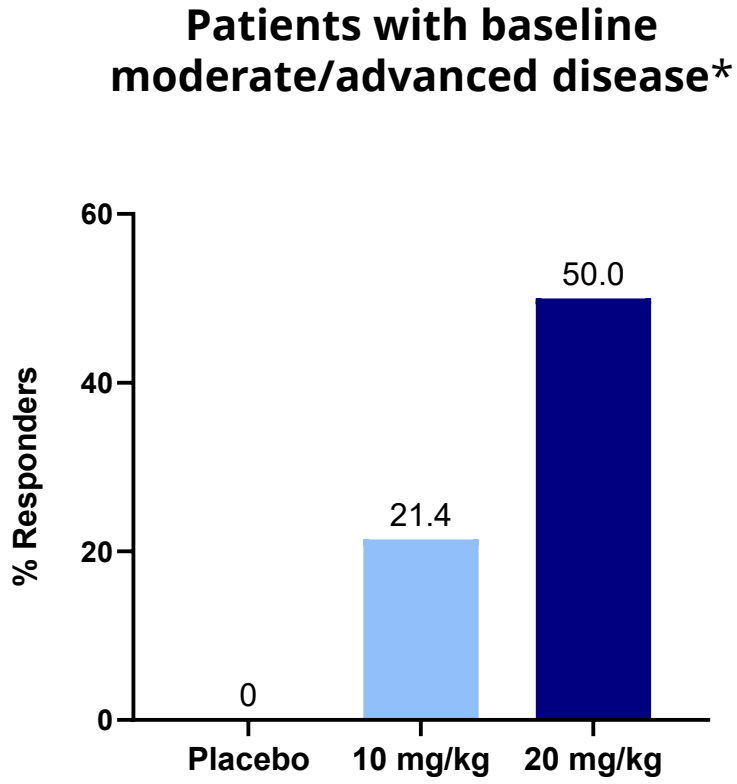
Nebokitug-treated patients experienced decreased pruritus scores across all timepoints compared to placebo

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

Results: Responder Analysis

Response was defined as any reduction in LSM, PRO-C3, and less than 0.19 increase in ELF score





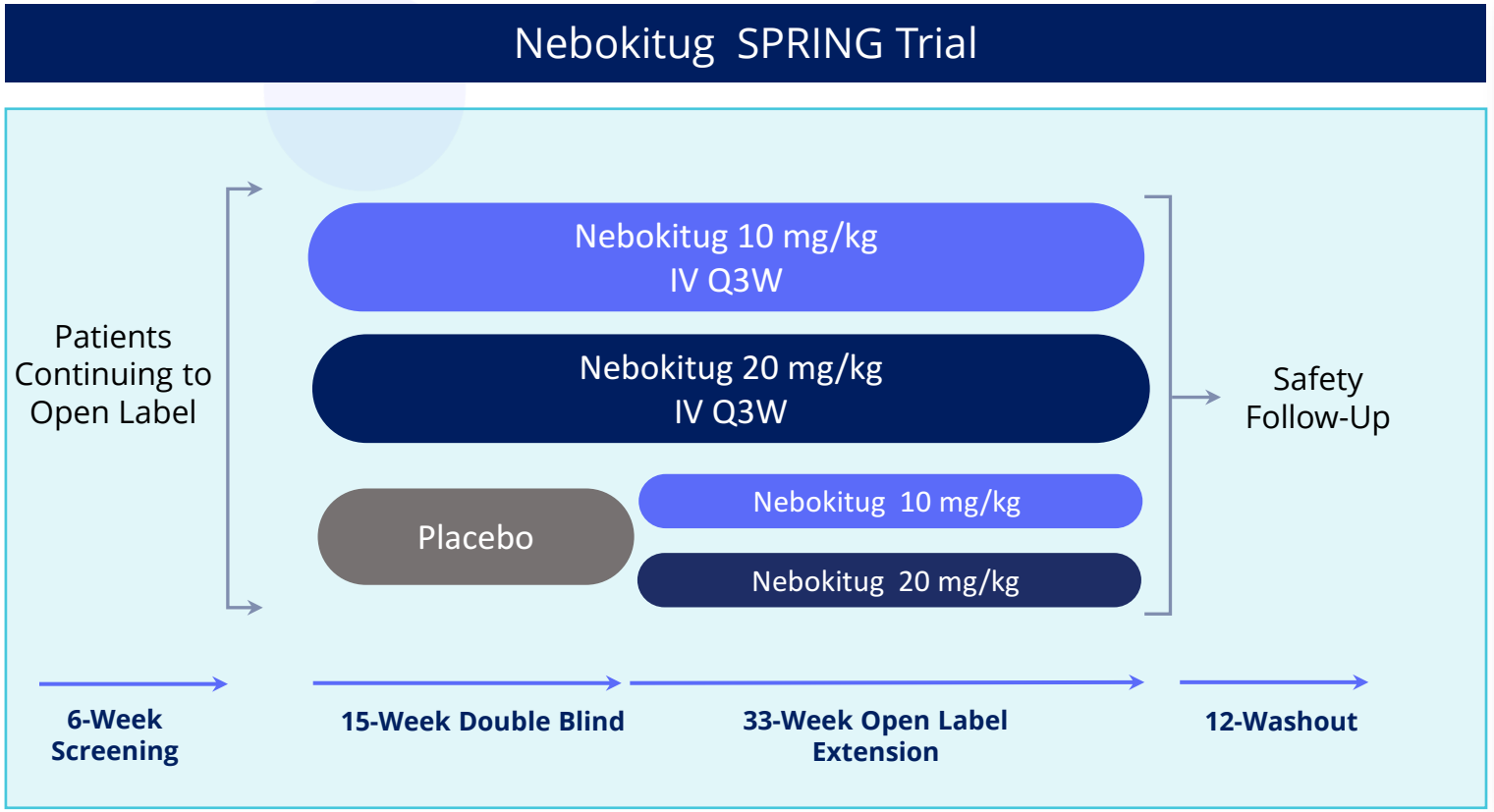
Summary of Findings from Double-Blind Period of the SPRING Study

- Nebokitug was well tolerated and had a safety profile comparable to placebo
- Nebokitug demonstrated dose dependent, anti-inflammatory, anti-fibrotic, and anti-cholestatic effects in patients with PSC
- In a pre-specified subgroup of patients with moderate to advanced disease, patients treated with nebokitug showed broad and consistent improvement in biomarkers associated with clinical outcomes

SPRING Study – Open Label Extension

SPRING Study: Open-label Design and Endpoints

93% of eligible patients elected to continue to Open Label Extension (OLE)



- Data from 48-weeks of nebokitug treatment were used to evaluate:
  - Long term safety
  - Durability of anti-fibrotic effects
  - Activity in the target population for Phase 3-- patients with moderate/advanced disease without cirrhosis
  - <u>Confirm the dose selected for Phase 3 (20mg/kg)</u>

50 of 54 patients eligible to participate in the Open Label Extension elected to continue; Most of the patients eligible to participate in the OLE were from the 20mg/kg group, reflecting the fact that the OLE was added to the protocol when many in the 10 mg/kg dose arm had already completed the study

Results: Safety and Tolerability – OLE Period

Treatment Emergent Adverse Events N, (%)	Placebo to Nebokitug 10mg/kg n=1	Placebo to Nebokitug 20mg/kg n=11	Nebokitug 10mg/kg n=11	Nebokitug 20mg/kg n=27
	Total 33 weeks exposure		Total 48 weeks exposure	
Treatment Emergent Adverse Events (TEAE)	1 (100%)	9 (81.8%)	9 (81.8%)	25 (92.0%)
Related to study drug	1 (100%)	5 (45.5%)	5 (45.5%)	10 (37.0%)
Serious TEAE	1 (100%)	0	2 (18.2%)	0
*Related to study drug	1	0	1	0
TEAE leading to death	0	0	0	0
TEAE leading to treatment discontinuation	0	0	2 (18.2%)	1 (3.7%)

Nubokitug continued to be well tolerated, and no new safety signal was observed

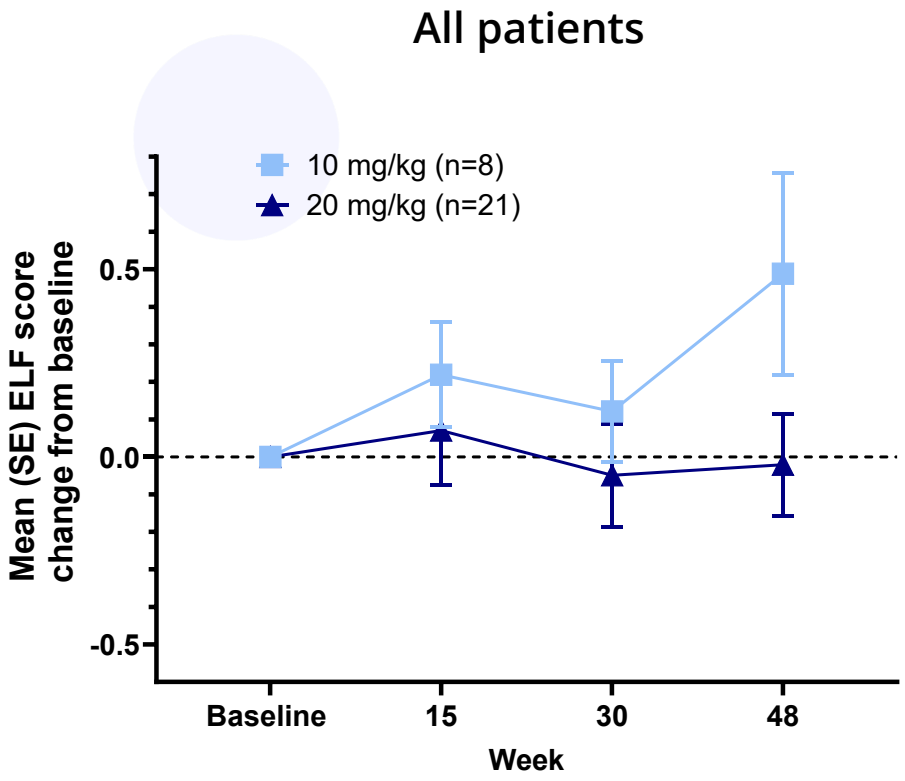
*The two serious TEAEs that were possibly drug-related were acute cholangitis and gallstone pancreatitis

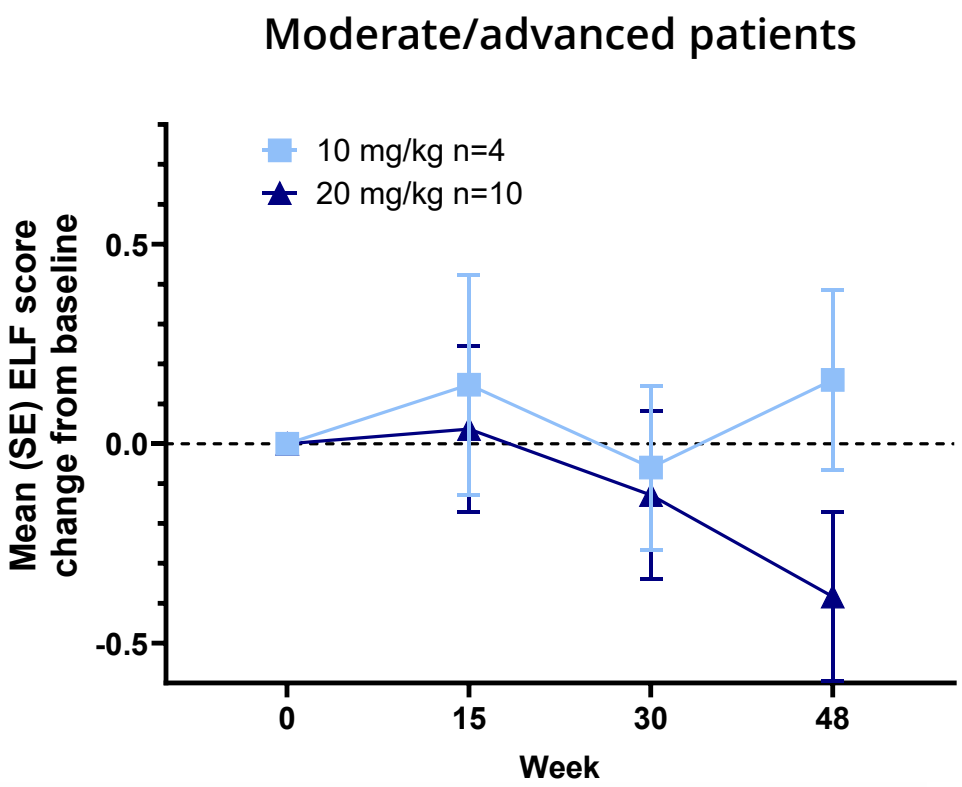
Results: Safety and Tolerability – OLE Period

Treatment Emergent Adverse Events, n (%) ≥10% Frequency	Placebo to Nebokitug 10mg/kg n=1	Placebo to Nebokitug 20mg/kg n=11	Nebokitug 10mg/kg n=11	Nebokitug 20mg/kg n=27
	Total 33 weeks exposure		Total 48 weeks exposure	
Fatigue	0	1 (9.1%)	1 (9.1%)	8 (29.6%)
Pruritus	0	3 (27.3%)	2 (18.2%)	6 (22.2%)
Nasopharyngitis	0	2 (18.2%)	0	6 (22.2%)
Headache	0	1 (9.1%)	0	5 (18.5%)
Diarrhea	0	0	1 (9.1%)	4 (14.8%)
Influenza	0	3 (27.3%)	0	2 (7.4%)
Upper respiratory tract infection	0	2 (18.2%)	0	2 (7.4%)
Abdominal pain	0	2 (18.2%)	1 (9.1%)	0
COVID 19	0	0	3 (27.3%)	0
Nausea	0	2 (18.2%)	0	1 (3.7%)

Nubokitug continued to be well tolerated, and no new safety signal or off-target effects was observed

Results: ELF Scores – OLE Period

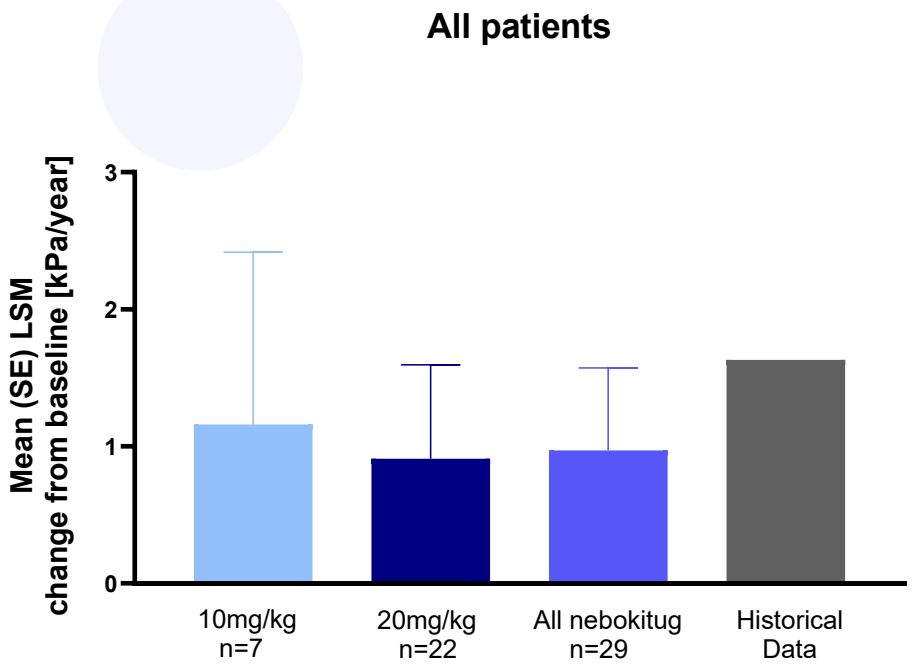


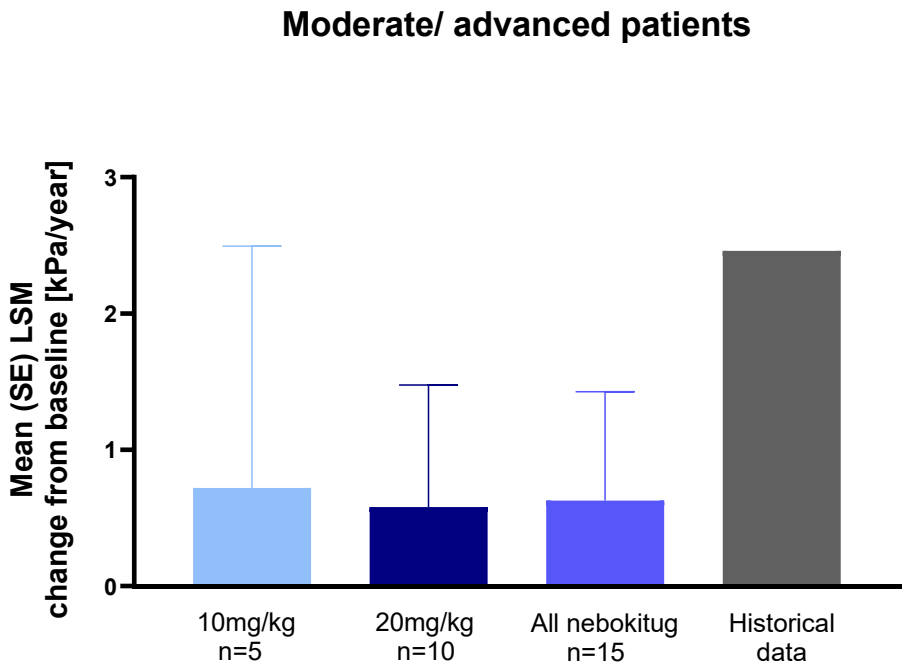


Continual reduction in ELF score was observed in patients with moderate/ advanced disease

All Patients-Defined as all open label completers; Moderate/advanced patients (ELF≥9.8 at baseline)

Results: Liver Stiffness Measurements – OLE Period





Sustained LSM reduction from week 15 to week 52 was observed suggesting nebokitug may slow disease progression

All patients included all study completers who had an LSM at baseline and Week 48
Moderate/Advanced patients by LSM between 8.7 and 14.4kPa
Historical data derived from Corpechot C, et al. Gastroenterology 2014;146:970

Key Findings from the Open-Label Extension Period of the SPRING study

- Safe and well-tolerated for up to 48 weeks of treatment
- Showed sustained or continual improvement in markers of fibrosis
  - Sustained and continual reduction in ELF score, especially in patients with moderate/advanced disease receiving nebokitug 20mg/kg
  - Stabilization of liver stiffness as measured by VCTE, especially in patients with moderate/advanced disease receiving nebokitug 20mg/kg

– These findings support developing nebokitug 20mg/kg in a phase 3 clinical study in patients with PSC

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