Phase 2a study of CM-101, a CCL24 neutralizing antibody, in patients with nonalcoholic steatohepatitis: A proof-of-concept study

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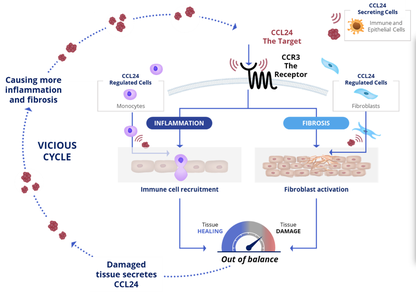
Chemomab THERAPEUTICS

Background

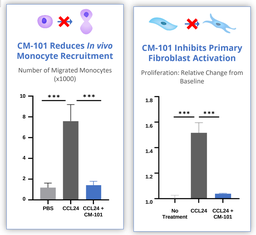
Rationale for Targeting CCL24-CCR3

CCL24 (eotaxin-2) is a chemokine that promotes cell trafficking and regulates inflammatory and fibrotic activities through the CCR3 receptor. It plays a central role in driving hepatic fibrosis and liver injury.



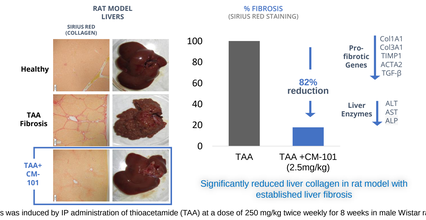
Mechanism of Action of CM-101

CM-101, a humanized IgG1 anti-human CCL24 monoclonal antibody, has been shown in pre-clinical models to significantly reduce migration and activation of immune cells and fibroblasts, including hepatic stellate cells



Preclinical data of CM-101 in Liver Fibrosis

CM-101 Reduces Liver Fibrosis by >80% in TAA Mode*I



Significantly reduced liver collagen in rat model with established liver fibrosis

*Liver fibrosis was induced by IP administration of thioacetamide (TAA) at a dose of 250 mg/kg twice weekly for 8 weeks in male Wistar rats (10-12 weeks of age). Rats (n=10/group) received either vehicle control, or CM-101 2.5mg/kg IV twice weekly during weeks 4-8 (following established fibrosis) and were sacrificed at Week 8.

Methods

Overall Study Design

This was a single country, multi-center, double-blinded, randomized, placebo-controlled trial in patients with non-cirrhotic NASH and biopsy-confirmed F1c-F3 fibrosis

Total Study Duration 20 weeks

6-Week Screening	14-Week (8 administrations) Double-blind Treatment Period	6-week Follow-up
N =23 patients 2:1 (Active vs. Placebo)	CM-101 5mg/kg SQ Q2W (n=14)*	Post-dosing safety follow-up
	Placebo SQ Q2W (n=9)*	

*Intention to treat population

Study Endpoints

Primary Endpoint:
- Safety and tolerability of CM-101 in subjects with NASH as assessed by adverse events and serious adverse events

Selected Secondary Endpoints:
- CM-101 Serum PK profile
- Development of anti-drug antibodies (ADA)
- Change from baseline in serum biomarkers for NASH pathogenesis, inflammatory, fibrotic and pharmacodynamic parameters
- Change from baseline in liver stiffness

References

Mor A, et al. Ann Rheum Dis. 2019;78:1260.
Segal-Salto M, et al. JHEP Rep. 2020;2:100064.
Taru M-G, et al. Diagnostics. 2023; 13:788.

Methods

Key Inclusion Criteria

- Male or Female; Age 18-75 years
- Histological confirmation of steatohepatitis and fibrosis without cirrhosis on a diagnostic liver biopsy obtained within the 18 months prior to randomization, with a NAS score ≥ 4 with a score of at least 1 for each component (steatosis, ballooning degeneration, and lobular inflammation), and with hepatic fibrosis stage 1C, 2 or 3 as defined by the NASH CRN scoring scale
- Presence of ≥ 10% steatosis on MRI-derived proton-density fat-fraction (PDFF)
- Confirmation of disease status from time of biopsy by Transient Elastography with liver stiffness value of 7-12 kPa
- Body mass index between 25-45 kg/m²

Key Exclusion Criteria

- History or presence of cirrhosis (compensated or decompensated) determined by histology or relevant medical complications and laboratory parameters
- Evidence of drug induced steatohepatitis secondary to medications known to cause hepatic steatosis
- Model for End-stage Liver Disease (MELD) score >12
- History of liver transplant, or current evaluation for or placement on a liver transplant waiting list
- History or evidence of any of the following: Alcoholic liver disease, Hepatitis B, Hepatitis A, autoimmune hepatitis, PBC, PSC, Wilson's Disease, alpha-1-antitrypsin deficiency , hemochromatosis, drug-induced liver disease, malignancy

Results

Baseline Characteristics

	CM-101 (N=14)*	Placebo (N=9)*
Demographics		
Age (Years)	53.8 (11.4)	46.6 (16.8)
Female gender (%)	6 (42.9%)	6 (66.7%)
White (%)	14 (100%)	9 (100%)
Liver Enzymes		
Alanine Aminotransferase (U/L)	33.8 (13.0)	29.5 (6.5)
Aspartate Aminotransferase (U/L)	45.8 (25.8)	45.6 (23.1)
Lipids		
Triglycerides – mg/dL	142.8 (52.1)	157.6 (67.9)
LDL-Cholesterol – mg/dL	93.2 (30.5)	112.1 (32.7)
Type 2 Diabetes Mellitus	**10 (76.9%)**	**3 (33.3%)**
NAFLD Activity Score (NAS)	**4.6 (1.5)**	**4.8 (0.8)**
FAST Score	**0.53 (0.23)**	**0.34 (0.19)**

	CM-101 (N=14)*	Placebo (N=9)*
Liver Disease Severity		
Fibrosis Stage 1a	0 (0%)	1 (11.1%)
Fibrosis Stage 1c	6 (42.9%)	5 (55.6%)
Fibrosis Stage 2	3 (21.4%)	3 (33.3%)
Fibrosis Stage 3	5 (35.7%)	0 (0%)
MELD Score	7.7 (2.6)	6.8 (2.0)
Liver Imaging		
**Liver Stiffness* E(kPa)	11.5 (5.2)	8.4 (1.1)
""Liver fat percentage (%)	19.0 (7.0)	18.7 (6.3)
Biomarkers		
ELF score	9.8 (0.9)	8.6 (0.3)
Pro-C3 (ng/mL)	40.0 (8.9)	31.3 (5.8)
Fibrosis-4 (FIB4) score	1.5 (1.2)	0.7 (0.3)
C-reactive protein (CRP) (mg/dL)	1.2 (1.0)	0.6 (0.6)
Serum CCL24 (pg/ml)	1101 (852)	880 (883)
Neutrophil – Lymphocyte Ratio (NLR)	2.29 (0.86)	1.51 (0.39)

Data presented as n (%) or mean (SD) unless otherwise stated
NAFLD = Nonalcoholic fatty liver disease; FAST = FibroScan-AST
* Analysis was per protocol population (CM-101 n=13, Placebo n = 8)
ELF = Enhanced Liver Fibrosis
** By VCTE, FibroScan; "" by MRI-PDFF

Safety and Tolerability

- **CM-101 5mg/kg SQ every 2 weeks for 14 weeks was safe and well tolerated.**
- **Most adverse events (AEs) were mild with one unrelated serious adverse event.**
- **No ADAs were detected at 20 weeks.**

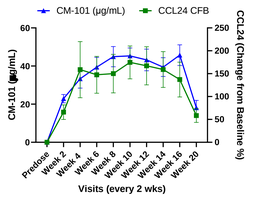
Adverse Events	CM-101 (N=14)	Placebo (N=9)
Any TEAEs*	10 (71.4%)	8 (88.5%)
Any Related TEAEs	5 (35.7%)	6 (66.7%)
Any SAEs	1 (7.1%)	0 (0%)
Any Related SAEs	0 (0%)	0 (0%)

*TEAEs- Treatment emergent adverse events; "SAEs –Serious adverse events

Injection site erythema and injection site pruritis were the most frequently reported TEAEs in the CM-101 group 21.9% and 6.3%, respectively compared to placebo 0% and 0%, respectively.

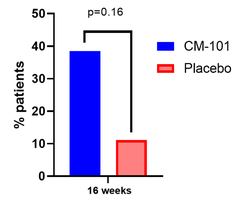
Target Engagement

CM-101 demonstrated a favorable PK-target engagement profile



Effects on Liver Stiffness

Percentage of subjects with reduction in at least one fibrosis stage

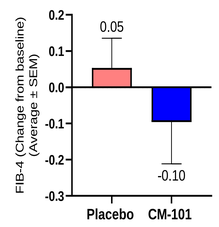


Fibrosis Staging by FibroScan® (kPa)

F0 - F1	F2	F3	F4
2 - 8.5	8.5 - 9.5	9.5 - 13.5	>13.5

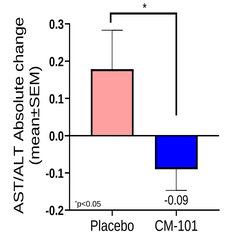
Changes in FIB-4 Score

CM-101 was associated with reductions in FIB-4 Score



Changes in AST/ALT Ratio

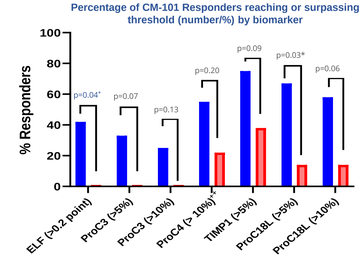
CM-101 was associated with reductions in AST/ ALT Ratio



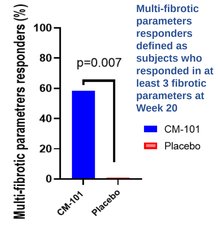
Effects on Fibrosis Biomarkers

CM-101 was associated with improvements in multiple fibrosis markers

Percentage of CM-101 Responders reaching or surpassing threshold (number/%) by biomarker



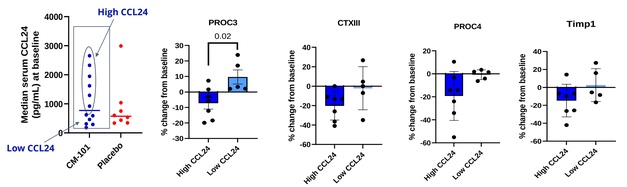
Multi-fibrotic parameters responders defined as subjects who responded in at least 3 fibrotic parameters at Week 20



N=12 active, 8 placebo per protocol population analysis; *p ≤0.05; ++ Measured at week 16. The other biomarkers were measured at week 20.
ELF- enhanced liver fibrosis score, consists of TIMP-1, amino-terminal pro-peptide of type III procollagen (PRINP) & hyaluronic acid; ProC3-procollagen 3; ProC4-procollagen 4; TIMP1-tissue inhibitor of metalloppeptidase; ProC18L-procollagen 18L

Associations between CCL24 levels and fibrosis markers

CM-101 treated subjects with high CCL24 levels at baseline had greater biomarker responses than those with lower CCL24 levels and were likely to be multiple responders



Threshold defined as CCL24 baseline median of 610 pg/ml
High CCL24 defined as >610 pg/mL; Low CCL24 defined as <610 pg/mL

Conclusions

- CM-101 (5mg/kg) administered SQ every 2 weeks for 14 weeks was safe and well tolerated.
- CM-101 demonstrated a favorable PK-target engagement profile
- CM-101 was associated with improvements in multiple fibrosis markers
- CM-101 was associated with a reduction in liver stiffness stage, FIB-4 Score, and AST/ALT Ratio
- Neutralizing the pro-inflammatory and pro-fibrotic effects of CCL24 with CM-101 at higher doses and for a prolonged duration merits further study
- Results from this study provided evidence supporting CCL24 as a potential therapeutic target in NASH.

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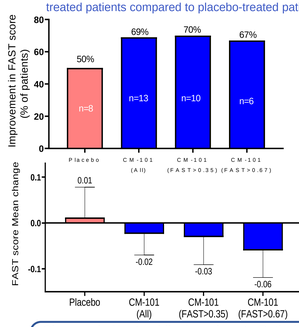
Subgroup Analysis by FibroScan-AST FAST Score

- To further explore the potential of anti-fibrotic effects of CM-101 in patients with NASH, post-hoc analyses were conducted in subgroups categorized by FAST score
- CM-101 treated patients were categorized by FAST Score > 0.35 (n=10) and FAST Score >0.67 (n=6)

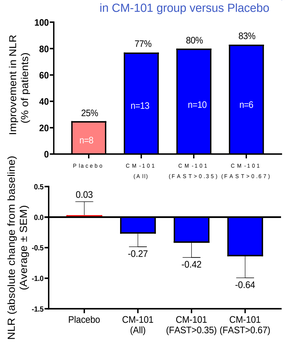
FAST Score

FAST score improved in a higher proportion of CM-101-treated patients compared to placebo-treated patients



Changes in Neutrophil – Lymphocyte Ratio (NLR)

Inflammation-related biomarker NLR was improved in CM-101 group versus Placebo



Changes in ProC-3

Pro-C3 improved in a higher proportion of CM-101-treated patients compared to placebo-treated patients