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Targeting CCL24 in primary sclerosing cholangitis with CM-101: rationale and study design

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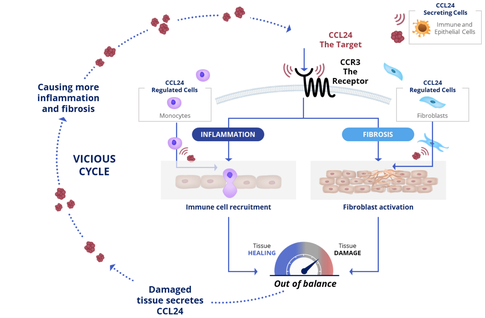
Background

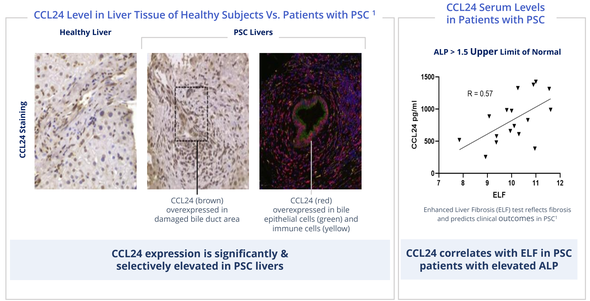
Primary sclerosing cholangitis (PSC) is a rare, chronic cholestatic liver disease characterized by progressive inflammation, fibrosis, and destruction of the intrahepatic and extra-hepatic bile ducts. Animal models of PSC have shown that cytokines and chemokines may be important pathogenetic mediators of liver inflammation and fibrosis.

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



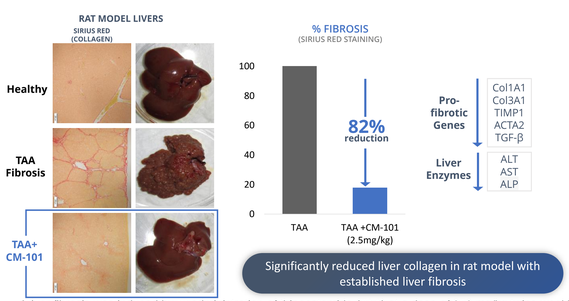
CCL24 plays a key role in PSC pathogenesis



Pre-Clinical Data of CM-101 Targeting CCL24

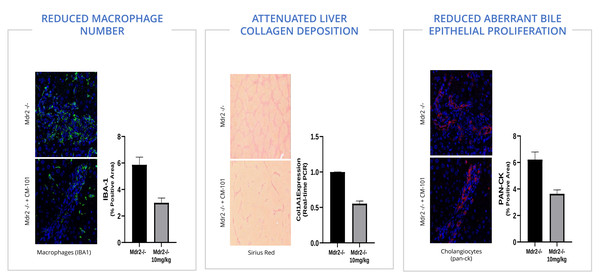
CM-101, a humanized IgG1 anti-human CCL24 monoclonal antibody, has been shown in pre-clinical models to significantly reduce migration and activation of immune cells and fibroblasts, including hepatic stellate cells

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



*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.

CM-101 Reduces Liver Injury and Fibrosis in PSC model



Methods

We are currently conducting a Phase 2a, randomized, double-blind, placebo-controlled, multiple-dose, international study to understand the role of CCL24 in the pathogenesis of PSC, the effects of blockade of CCL24 with CM-101, and evaluate the safety and tolerability of CM-101 in adult patients with PSC. (NCT04595825).

Overall Study Design

6-Week Screening	15-Week Double-Blinded Treatment Period	33-Week Open Label Treatment Period	12-Week Follow-up
N ~ 68 patients 5:2 (CM-101 vs. Placebo)*	Placebo IV Q3W (n=18)	CM-101 10mg/kg IV Q3W	Post-dosing safety Follow-up
	CM-101 10mg/kg IV Q3W (n=25)		
	CM-101 20mg/kg IV Q3W (n=25)	CM-101 20mg/kg IV Q3W	

*Protocol Version 4.0

Key Eligibility Criteria

- Age 18 – 75 years
- Large duct PSC of >24 weeks duration
- ALP > 1.5 x ULN
- Stable IBD allowed
- Stable UDCA treatment allowed
- Stable vancomycin for PSC allowed
- Stable biologics allowed

Study Endpoints

Primary Endpoint:
Safety and tolerability assessments

Secondary Endpoints:
Change from baseline to Week 15:
- Serum ALP
- Liver enzymes (AST, ALT, GGT)
- ELF score
- Liver fibrosis biomarkers (e.g., PRO-C3, PRO-C5)
- Pharmacokinetic profile
- Pharmacodynamic parameters

Exploratory Endpoints:
Change from baseline to Week15 in:
- CCL24, chemokines and cytokines levels
- Serum inflammatory markers (e.g. hsCRP, MCP1, IL-1, IL-6)
- Liver stiffness (FibroScan)

Change from baseline to Week 48 in ALP, liver enzymes, ELF scores, other biomarkers, and liver stiffness

Results

- This trial is ongoing.
- The Data Monitoring Committee met in May 2023 and had no safety concerns.

Conclusions

- Results of this trial are expected in the latter half of 2024 and will further elucidate the role of CCL24 in inflammatory and fibrotic disease pathology, and the clinical impact of CM-101 in reducing the over expression of CCL24 in PSC. This will guide future development of CM-101 in PSC.

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References

Mor A, et al. Ann Rheum Dis. 2019;78:1260; Segal-Salto M, et al. JHEP Rep. 2020;2:100064.