CM-101 A NOVEL CCL24 BLOCKING MONOCLONAL ANTIBODY DEMONSTRATES SAFETY, TARGET ENGAGEMENT AND LONG HALF- LIFE IN A PHASE 1 RANDOMIZED, CONTROLLED SINGLE ASCENDING DOSE TRIAL USING IV AND SC FORMULATIONS IN HEALTHY SUBJECTS

ARNON AHARON[1], MICHAL SEGAL-SALTO[1], NETA BARASHI[1], SHARON HASHEMUELI AND ADI MOR[1]

[1] Chemomab Ltd. Tel-Aviv

AASLD November 13-16, 2020 The Liver Meeting® Digital Experience

Background

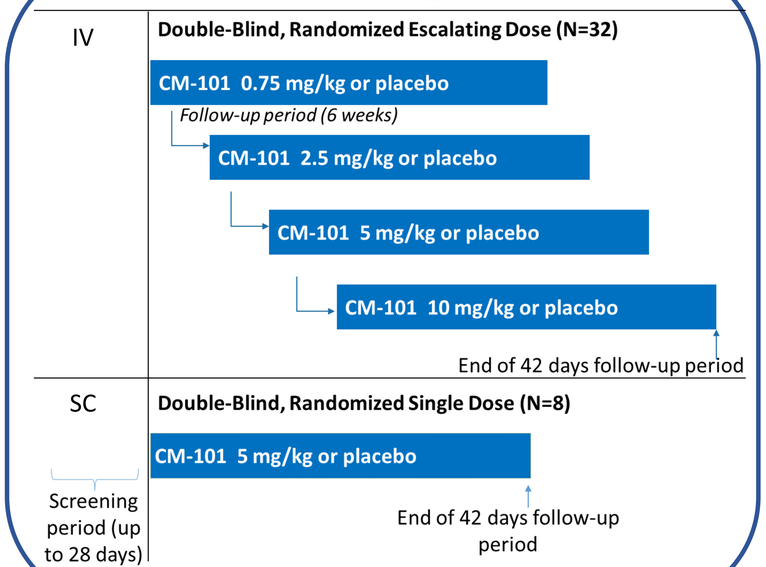
CM-101 is a fully humanized monoclonal antibody that binds and neutralizes its soluble target CCL24 with high affinity, preventing its binding to the CCR3 receptor and blocking CCR3-CCL24 dependent signaling. CM-101 was shown to improve fibrosis and liver damage in animal models of primary sclerosing cholangitis (PSC) and nonalcoholic steatohepatitis (NASH).

CCL24 is a novel fibrotic target shown to play a pivotal role in the development of liver fibrosis and inflammation in-vitro and in-vivo. CCL24 is a member of the chemokine family and is prominently expressed in PSC and NASH liver biopsies. In patients, serum levels of CCL24 correlates with disease severity and clinical outcome.

Methods

Chemomab conducted a first-in-human Phase 1, double blind, randomized, placebo controlled, single-administration study. This study randomized 40 healthy male subjects in a 3:1 CM-101 to placebo ratio. The aim of the study was to assess safety, tolerability, PK, immunogenicity and target engagement following a single ascending CM-101 dose. Subjects received CM-101 as a single escalating intravenous (IV) infusion of 0.75 mg/kg, 2.5 mg/kg, 5 mg/kg and 10 mg/kg (N=24) or single subcutaneous (SC) dose of 5 mg/kg (N=6) or matching placebo (N=10). Subjects were followed for 42 days post administration. CM-101 levels in serum were measured by specific ELISA. CCL24 serum levels were quantified by a validated ELISA.

Study Design



Conclusion

CM-101 is a novel CCL24 blocking antibody that is in development for treatment of inflammatory-fibrotic diseases. In this phase 1 single administration study in healthy subjects, IV or SC doses up to 10 mg/kg were safe and well tolerated, with a favorable PK profile supporting a once every 2-4 weeks dosing. CM-101, within the tested dose range, efficiently binds its soluble target (CCL24), as reflected by target engagement, supporting its ability to block CCR3-CCL24 dependent signaling.

CM-101 completed a phase 1b multiple administration study in NAFLD patients and is currently being tested in a Phase 2a study in PSC.

Results

Safety

Subjects mean age was 25.5±5.2 years and all were males. No differences in demographics or laboratory parameters between the pooled CM-101 treated subjects (N=30) and placebo (N=10) were noted.

CM-101 was safe and well tolerated in all tested doses and formulations. All reported AEs were mild or moderate and the most common were headache, changes in diastolic blood pressure and rhinitis. No DLTs were reported and none of the subjects developed anti-drug antibodies. No injection site reactions were reported for both IV and SC formulations.

	CM-101								Placebo		All	
	0.75 mg/kg		2.5 mg/kg		5.0 mg/kg		10.0 mg/kg					
IV Administration	Subjects N=6	AEs	Subjects N=6	AEs	Subjects N=6	AEs	Subjects N=6	AEs	Subjects N=8	AEs	Subjects N=32	AEs
AEs	6 (100)	22 (100)	3 (50)	8 (100)	3 (50)	17 (100)	5 (83.3)	15 (100)	6 (75)	22 (100)	23 (71.9)	84 (100)
Drug-related AEs (possibly)	2 (33.3)	5 (22.7)	0	0	2 (33.3)	2 (11.7)	3 (50)	4 (26.6)	3 (37.5)	6 (27.2)	10 (31.3)	17 (20.2)

	CM-101		Placebo		All	
	5.0 mg/kg					
SC Administration	Subjects N=6	AEs	Subjects N=2	AEs	Subjects N=8	AEs
AEs	2 (33.3)	6 (100)	0 (0)	0 (100)	2 (25)	6 (100)
Drug-related AEs (possibly)	1 (16.7)	1 (16.7)	0 (0)	0 (0)	1 (12.5)	1 (16.7)

Table 1 – Distribution of drug related AEs across different CM-101 doses, administration modes and Placebo. No differences in AEs distribution between the different CM-101 doses or Placebo were noted.

Pharmacokinetics

CM-101 pharmacokinetic profile was dose proportional, with an average $T_{1/2}$ of about 21 days for both formulations.

Comparing the IV and SC formulations (using the 5 mg/kg dose) demonstrated a matching and adequate exposure profile supporting the ability to use both formulations in future clinical studies. CM-101 serum levels at 2.5-10 mg/kg dose range reached the exposure that was associated with activity in animal models of liver injury and fibrosis.

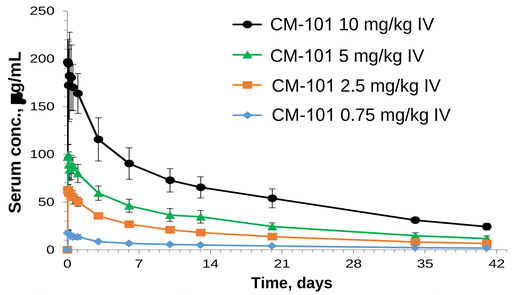


Figure 1 – CM-101 average serum concentrations vs. time in IV treatment.

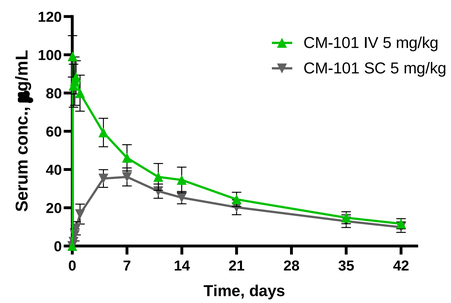


Figure 2 – CM-101 5 mg/kg average serum concentrations in both IV and SC administrations.

Pharmacodynamics

Target engagement was evaluated by measuring serum CCL24 at matching time points to PK analysis. A dose proportional increase in serum CCL24 levels was demonstrated matching the CM-101 PK profile, indicating sequestration of CCL24 by CM-101 and formation of ligand-antibody complexes. The CM-101-CCL24 complexes once formed are inactive, therefore blocking CCR3-CCL24 dependent signaling.

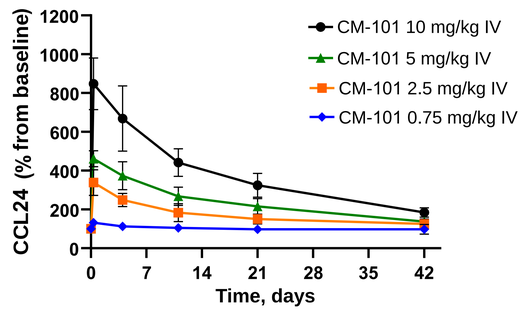


Figure 3 – Target engagement presented as CCL24 (% change from baseline) over time for the different CM-101 doses in IV treatment.

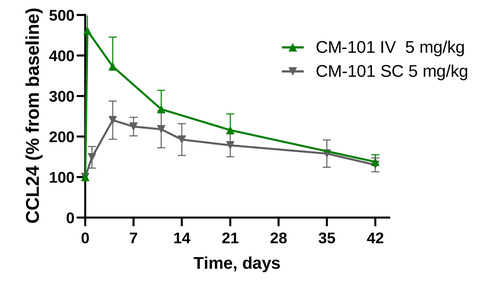


Figure 4 - Target engagement presented as CCL24 (% change from baseline) over time for CM-101 5 mg/kg in both IV and SC administrations.