Clinical tolerability and safety profile of CER-001, a novel bio-engineered pre-β HDL-mimetic, across the clinical development programme

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Background

- The main protective effect of high-density lipoprotein (HDL) against atherosclerosis is its ability to emulate reverse lipid transport, to mobilise lipids from lipid-rich atherosclerotic plaques and to promote faecal cholesterol excretion
- Cerenis Therapeutics has developed CER-001, an engineered discoidal particle comprising recombinant human apolipoprotein A-I (ApoA-I) and phospholipids mimicking the structure and functions of natural nascent, discoidal pre-β HDL particles
- In preclinical studies, CER-001 promotes cholesterol efflux from macrophages and regresses atherosclerotic plaques[1]
- Clinical trials in patients with familial hypercholesterolaemia or hypoalphalipoproteinaemia, showed CER-001 reduced carotid wall thickness and enhanced faecal cholesterol excretion, thus reducing atherosclerotic burden[2,3]
- Encouraging efficacy results have been reported with CER-001 in patients with acute coronary syndrome (ACS)[4,5] in the ongoing clinical development programme

Purpose

- To report the clinical tolerability and safety findings seen with CER-001 across the clinical development programme, to date
- To determine whether any specific treatment-related adverse events (AEs) emerge as clinical experience with the product increases

Methods

Design

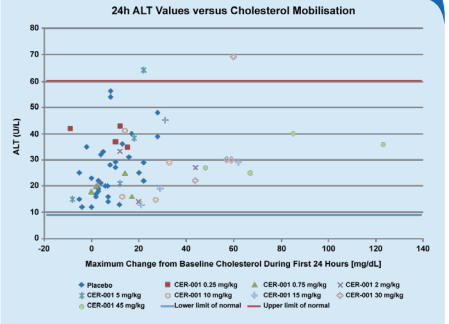
- Across the Phase I/II clinical development programme, AE, serious AE (SAE) and other safety-related data were collated to evaluate the safety profile of CER-001
- Phase I:
  - randomised, double-blind, placebo-controlled, cross-over, single rising-dose study in healthy volunteers with an LDL/HDL ratio >3.0;
  - CER-001 single intravenous (IV) escalating dose of 0.25, 0.75, 2, 5, 10, 15, 30 and 45 mg/kg
- Phase II:
  - multiple-dose comparator studies involving CER-001 (3–12 mg/kg), in patients with either ACS, familial hypercholesterolaemia or hypoalphalipoproteinaemia

Results

Phase I

- Thirty-two subjects were treated in 4 cohorts of 8 subjects; 31 (97%) subjects completed the study and 1 was lost to follow-up 3 weeks after receiving a single dose of CER-001
- All doses of CER-001 (0.25 to 45 mg/kg) were well tolerated, with an AE profile similar to that observed with placebo
- There were no SAEs or AEs that led to withdrawal, nor were there any deaths
- Effects on clinical chemistry, haematology and coagulation parameters were comparable with placebo, including effects on liver enzymes
- No adverse effects of CER-001 on ECGs were observed
- No antibodies to ApoA-I were detected following single dose administration of CER-001
- Mobilisation of free cholesterol in the HDL fraction was seen with CER-001 doses as low as 2.0 mg/kg (indicating efficacy; data not shown). Mobilisation of cholesterol, even at high doses, was not associated with significant elevation of liver enzymes (Figure 1)

Figure 1. ALT values are independent of cholesterol mobilisation



Phase II

- In multiple-dose studies involving CER-001(3–12 mg/kg), there have been no unusual or concerning AEs reported to date. After six administrations, one each week, in post-ACS patients, no antibodies against ApoA-I were detected at 6 months
- AE data from 530 subjects in Phase II studies, including type and incivdence of AEs, SAEs and AEs causing withdrawal from study treatment, show a safety profile for CER-001 that is comparable with placebo (Table 1) except for infusion reactions, which were more frequent with CER-001

Table 1. Most frequently (≥5%) AEs in double-blind comparator studies

AE, n (%)	Placebo (n=120)	CER-001 3 mg/kg (n=120)	CER-001 6 mg/kg (n=124)	CER-001 12 mg/kg (n=122)	All (n=486)
Angina pectoris	6 (5.0%)	10 (8.3%)	11 (8.9%)	8 (6.6%)	35 (7.2%)
Diarrhoea	3 (2.5%)	7 (5.8%)	4 (3.2%)	3 (2.5%)	17 (3.5%)
Nausea	8 (6.7%)	11 (9.2%)	4 (3.2%)	2 (1.6%)	25 (5.1%)
Fatigue	13 (10.8%)	12 (10.0%)	4 (3.2%)	13 (10.7%)	42 (8.6%)
Non-cardiac chest pain	6 (5.0%)	7 (5.8%)	5 (4.0%)	4 (3.3%)	22 (4.5%)
Cardiac procedure complication	6 (5.0%)	9 (7.5%)	3 (2.4%)	4 (3.3%)	22 (4.5%)
Dizziness	9 (7.5%)	4 (3.3%)	4 (3.2%)	4 (3.3%)	21 (4.3%)
Headache	11 (9.2%)	14 (11.7%)	10 (8.1%)	8 (6.6%)	43 (8.8%)
Cough	1 (0.8%)	6 (5.0%)	1 (0.8%)	1 (0.8%)	9 (1.9%)
Dyspnoea	3 (2.5%)	3 (2.5%)	6 (4.8%)	7 (5.7%)	19 (3.9%)
Hypertension	12 (10.0%)	15 (12.5%)	7 (5.6%)	8 (6.6%)	42 (8.6%)

- Treatment-related infusion reactions occurred in 16 of 410 subjects (4%) treated with CER-001 in Phase II studies. All cases were reversible and either resolved spontaneously or after management with antihistamines, steroids and/or IV fluids
- In studies evaluating liver enzymes (ALT, AST), there were no clinically relevant differences in elevations between CER-001 and placebo, with all elevations either resolving spontaneously or being attributed by the investigator to new/concomitant statin use in the post-ACS population
- The incidence of 3 times upper limit of normal (ULN) ALT elevations was low and there was no difference between CER-001 and placebo. There were no cases meeting Hy's Law (ALT > 3x ULN; bilirubin > 2x ULN)
- The incidence and type of SAEs were similar for CER-001 and placebo, with the possible exception of infusion reactions
- The single AE leading to death was mitral valve incompetence, which was considered by the treating physician, unlikely to be due to study treatment

Conclusions

- To date, CER-001 appears to have a clinical safety profile similar to placebo in terms of type and incidence of AEs, SAEs and AEs causing withdrawal from study treatment
- CER-001 was not associated with any adverse impact on hepatic safety
- Not unusually, a slightly higher incidence of infusion reactions has been reported and clinical study sites should be aware of the possibility of infrequent infusion reactions and be prepared to provide supportive care if necessary
- Safety results support continuing CER-001 clinical development for short- and long-term treatment

Declaration of Interest

AC received research grants, honoraria or has been a consultant for Merck, Novartis, AstraZeneca, Roche, Bristol-Meyers, Mylan, DOC, Pfizer, Kowa, Recordati, Amgen, Sanofi/Regeneron and Mediolanum
NF has nothing to declare
J-LD, RB, CK and RB are employees of Cerenis Therapeutics

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