A randomised double-blind dose escalation study to evaluate the safety and dose response of subcutaneous administration of coversin in healthy subjects

QUOTIENT CLINICAL
The Translational Pharmaceutics Company

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INTRODUCTION

Coversin is a small recombinant xenologous protein (16.8 kDa) which is derived from a native protein discovered in the saliva of the *Ornithodoros moubata* tick [1]. Coversin is an inhibitor of complement factor 5 (C5) activation. In tick saliva the function is to assist the parasite in feeding by suppressing the host immune reactions that would otherwise alert the host to the presence of the parasite which could then be removed by scratching or grooming.

Serum complement activity in some autoimmune diseases are elevated and hence inhibition of the C5 complement system is a therapeutic target in a wide range of autoimmune and inflammatory diseases including rheumatoid arthritis, Crohn's disease, hypersensitivity pneumonitis, ischaemia reperfusion injury, sepsis, myasthenia gravis, paroxysmal nocturnal haemaglobinurea and age related macular degeneration [2-9].

Pre-clinical PK studies in mice and rats indicated that complete ablation is achieved with an IV dose of 0.57 mg/kg. Thereafter, a dose of half that (0.285 mg/kg) infused over 12 h is sufficient to maintain total inhibition of terminal complement activity. Whilst this is an adequate way of treating acute conditions, it is not suitable for chronic conditions which do not required in-patient treatment.

OBJECTIVES

The objectives of this study were to assess the safety and tolerability of coversin administered via sub-cutaneous injection to humans, and to assess effect on complement inhibition to determine the dose to be used for future studies.

METHODS

- This was a randomised, double blind, single ascending dose study (Figure 1).
- Four groups of 6 healthy males were planned with each group comprising 4 subjects on active and 2 subjects on placebo.
- Potential subjects were screened for serum C5 complement activity in order to exclude hereditary complement deficiency.
- Subject who passed the initial screening procedures were immunised against *Neisseria meningitides* a minimum of 2 weeks before dosing and had nose and throat swabs taken for bacterial culture including *Neisseria meningitides* at least 5 days before dosing. Potential subjects who tested positive were excluded from the study.
- The starting dose was 1/8th of the highest dose calculated to result in total blockade of complement C5 and each successive dose escalation was 2-fold.
- The starting dose was well below 1/10th of the NOAEL.
- Doses were individualised to subject's weight.
- Subjects received subcutaneous injections (up to 1mL per injection) into the deltoid or quadriceps regions, with multiple injection sites used for higher doses.
- Dosing was performed in the morning after a light breakfast.
- Sentinel dosing of 1 active and 1 placebo was employed, with these subjects dosed 48 h in advance of the main group.
- Dosing of subjects in the main group was performed at 15 min intervals.
- In groups 1, 2 and 3 blood samples for serum complement activity were taken pre-dose and at 1 h post-dose.
- In group 4 blood samples for serum C5 complement activity were taken according to the following schedule:
  - pre-dose, 1, 3, 6, 12, 24, 48, 72 and 96 h post-dose
- All subjects were monitored for safety, including Holter monitoring for 8 h post-dose.
- Injection sites were inspected and graded on a scale of 0 – 3 and 1, 24 and 48 h post-injection. Any signs or symptoms were recorded as an AE.
- Subjects were permitted to leave the clinical unit at 48 h post-dose. Subject in group 4 returned to the unit at 72 and 96 h post-dose.
- A follow-up medical was performed at 7 ±2 days post-dose.

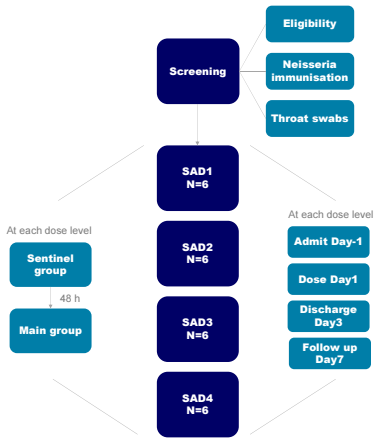

Figure 1: Study schedule

RESULTS

Subjects and safety

- 24 subjects completed the study. Six subjects (4 active, 2 placebo) were dosed at each of 4 dose levels (Table 1)
- There were no pre- to post-dose changes or abnormalities in safety assessments
- A total of 4 adverse events were reported – all were mild and transient.
- There was no statistical difference between the number and severity of AEs between active and placebo groups and no dose relationship in the frequency of AEs.

	Active	Placebo
N	16	8
Age (years)	33.4	32.9
Weight	81.8	78.5

Table 1: Demographic data (mean)

Pharmacodynamics

- Doses administered were:
  - Group 1: 0.07 mg/kg
  - Group 2: 0.14 mg/kg
  - Group 3: 0.28 mg/kg
  - Group 4: 0.57 mg/kg
- There was no significant difference in baseline complement activity between active and placebo (Figure 2).
- At 0.57 mg/kg serum complement activity fell to zero between 6 and 12 h post dose and remained below 10% for at least 24 h, rising to approximately 40% by 48 h post-dose.
- Differences between mean absolute complement activity and change from baseline were significant at the 99% confidence level at all time points from 3 to 72 h post-dose.
- Mean complement activity was 74% of baseline at 96 h post-dose.

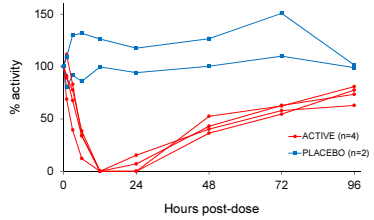

Figure 2: Percent complement activity change from baseline at 0.57 mg/kg (individual)

DISCUSSION

- The primary objective of this FIH study was to assess safety. Few AEs were reported and all were mild and transient. The data confirmed no evidence of first dose AEs of the kind frequently associated with the administration of a therapeutic monoclonal antibody.
- No injection site reactions or lymphadenopathy was observed.
- The effective dose (ED) of coversin was defined as that which resulted in lowering serum C5 complement activity to 75% of more of the baseline level in 3 of 4 active subjects treated at that dose.
- Pre-clinical data predicted that the the ED would be 0.57 mg/kg and this was confirmed in this FIH trial.
- The study showed that a single ablating dose of 0.57 mg/kg coversin achieved total complement inhibition between 6 and 12 h post-dose, and this was maintained until 24 h post-dose.
- In contrast, pre-clinical predictions of onset and duration of action were not confirmed.
- In murine PK studies, maximum complement inhibition was observed at 1 h post-dose and activity had returned to baseline within 24 h post-dose.
- In humans, maximum inhibition was observed between 6 and 12 h post-dose, and had not returned to baseline by 96 h post-dose.
- These data suggest a depot effect in humans that exceeds that seen in previous rodent PK studies, and that a maintenance dosing at 1 to 2 day intervals may be feasible.

CONCLUSION

The ED of coversin was found to be 0.57mg/kg, a dose level that was both safe and well tolerated. Single subcutaneous doses up to 0.57mg/kg were associated with few, mild AEs, the nature and severity of which appeared to have no dose relationship and no statistical difference between active and placebo.

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