Coversin, a novel C5 complement inhibitor, for the treatment of PNH: results of a Phase 2 clinical trial

Anita Hill1, Wynne Weston-Davies2, Jerzy Windygà3, Taduesz Robak1, Andrzej Hellman4, Morag Griffin5, Taha Munhir1, Anna Szmiigielka-Kaplón4, Agnieszka Piekar ska6, Miles Nun6

1Department of Haematology, St James’s University Hospital, Leeds, UK; 2Akari Therapeutics Plc, London, UK and New York, USA; 3Department of Disorders Haematosis and Internal Medicine, IHT Institut HaematoLOGi I Transfusiology, Warsaw, Poland; 4Department of Haematology, Medical University of Lodz, Poland; 5Department of Haematology and Transplantology, Medical University of Gdansk, Poland; 6Haematology Research Unit, University College London, UK

Introduction
Paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired life-threatening disease, characterized by complement-induced haemolysis and a high incidence of thrombosis. Coversin, a small (16.8 kDa) protein C5 complement inhibitor, originally derived from the haematophagous tick Ornithodoros moubata, is being developed as a therapy for PNH. Coversin is administered by subcutaneous injection and can be self-administered, making it possible for patients to treat themselves at home.

Following completion of Phase 1 clinical trials in healthy human volunteers, a Phase 2 open label 90 day trial was initiated December 2016. Enrolled patients had not previously received anti-complement therapy. Present study represents the first 4 patients to complete the Phase 2 trial.

The OBJECTIVES of the trial were to assess the safety and tolerability of Coversin, the efficacy of the dosing regime and whether self-injection by patients is well accepted.

Methods
All patients enrolled in the trial had a diagnosis of PNH confirmed by flow cytometry. Patients were eligible for inclusion whether or not they had a history of transfusion dependence. The lower age limit for inclusion was 18 years, with no upper age limit. A fixed dose regimen was used for all patients with weight limits of 50 – 100 kg. Patients were required to attend a haematology clinic for 2 days whilst Coversin therapy was initiated. After instruction, patients were encouraged to start self-injection as soon as possible. Nursing support at home was provided, if requested, for the first month of the trial.

Patients attended their investigator’s clinic at least weekly for the first month and then monthly until the end of the trial. Terminal complement activity and clinical response were monitored. All patients completed daily diary cards to record dosing and adverse events (AEs). EORTC-30 and EQ-5D-5L quality of life instruments were used to assess global health status.

Treatment started with an ablation phase consisting of a single 60mg injection followed by 3 doses of 30mg 12 hours apart. An inflation phase of 26 doses followed during which patients received 10mg 12 hourly doses. Upward titration to 22.5mg 12 hourly was allowed during this period in the event of inadequate clinical response. On Day 28, patients moved to a single dose of either 30mg or 45mg every 24 hours. The trial protocol permitted patients to continue Coversin therapy during this period in the event of inadequate clinical response. On Day 30 and EQ-5D quality of life instruments were used to assess global health status.

Results
Five patients have been enrolled in the study to date. Patient demographics are shown in Table 1. The duration between initial diagnosis and initiation of Coversin therapy ranged from 8.5 to 79 months (mean 44 months). Four patients completed the 90 day study per protocol and moved into the long-term safety and efficacy study. One patient (Patient E) with a suspected co-morbidity unrelated to the treatment was withdrawn from the study on Day 43.

All patients had a CH50 level below the limit of quantification (≤ 5000 U/mL) after the ablating phase initiatingisks at the terminal complement pathway (Fig 1, left).

The study drug was well tolerated and patients reported no difficulty with self administration. There were no serious adverse events (SAEs). The most common adverse events (occurring in > 10% of patients) were self-injection site reactions which declined towards the end of the trial. None of the AEs required specific treatment or were severe enough to cause discontinuation of the study drug. A full listing of AEs is shown in Table 2.

Conclusions

- None of the four patients required transfusion during the trial while 3 out of 4 patients required a total of 10 units PRBC during the 3 months preceding the trial (Figure 3, left). Patient A had no history of transfusion. Haemoglobin levels for the 4 patients are shown in Figure 3, right). For two patients (A and D), there was essentially no change in haemoglobin levels from Day 1 to Day 90. For the other two patients, haemoglobin levels increased by 19% (patient D) and decreased by 14% (patient C) from Day 1 to Day 90.

None of the four patients required transfusion during the trial while 3 out of 4 patients required a total of 10 units PRBC during the 3 months preceding the trial (Figure 3, left). Patient A had no history of transfusion. Haemoglobin levels for the 4 patients are shown in Table 4. For two patients (A and D), there was essentially no change in haemoglobin levels from Day 1 to Day 90. For the other two patients, haemoglobin levels increased by 19% (patient D) and decreased by 14% (patient C) from Day 1 to Day 90.

The study drug was well tolerated and patients reported no difficulty with self administration. There were no serious adverse events (SAEs). The most common adverse events (occurring in > 10% of patients) were self-injection site reactions which declined towards the end of the trial. None of the AEs required specific treatment or were severe enough to cause discontinuation of the study drug. A full listing of AEs is shown in Table 2.

The MDC score at initiation of therapy for all 5 patients, Coversin A, B, C, D and E, was 9.0. In the Phase 2 trial, Coversin D scored all categories 5 points greater than Coversin A, B, C, and E, all of which remained at 9 points, which was self-administered.

The objective was to enrol additional patients in this Phase 2 trial using a revised dosage plan. The plans to enrol additional patients in this Phase 2 trial using a revised dosage plan. Patients A, B, C and D were self-administered at 900 mg by subcutaneous injection by patients is well established.

To answer the clinical question of whether Coversin administration improves global health status, the EORTC-30 quality of life instrument, which was self-administered, all 5 patients developed low titre antibodies but no neutralising antibodies were observed.

Table 1: Patient Demographics

- Patient A: Mean age 58 years (range 36-70), Female, Weight 74 kg (range 60-94)
- Patient B: Mean age 58 years (range 36-70), Female, Weight 74 kg (range 60-94)
- Patient C: Mean age 58 years (range 36-70), Female, Weight 74 kg (range 60-94)
- Patient D: Mean age 58 years (range 36-70), Male, Weight 74 kg (range 60-94)
- Patient E: Mean age 58 years (range 36-70), Female, Weight 74 kg (range 60-94)

Table 2: Adverse Events

- Injection site reaction in 22.5% (4/18) of patients
- Rash in 22.5% (4/18) of patients
- Hypersensitivity reactions in 22.5% (4/18) of patients
- Transient decrease in Hb of 1% (1/18) of patients
- For the 4 patients (A, B, C and D) at Day 28 required transfusion during the 3 months preceding the trial (Figure 3, left).

- Patient A had no history of transfusion. Haemoglobin levels for the 4 patients are shown in Table 4.

- For two patients (A and D), there was essentially no change in haemoglobin levels from Day 1 to Day 90. For the other two patients, haemoglobin levels increased by 19% (patient D) and decreased by 14% (patient C) from Day 1 to Day 90.

- The study drug was well tolerated and patients reported no difficulty with self administration. There were no serious adverse events (SAEs). The most common adverse events (occurring in > 10% of patients) were self-injection site reactions which declined towards the end of the trial. None of the AEs required specific treatment or were severe enough to cause discontinuation of the study drug. A full listing of AEs is shown in Table 2.

- All four patients who completed the trial remain on Coversin therapy.

- In this trial, an ascending dose design was used for reasons of safety. All four patients experienced complete terminal complement inhibition. Dose increases were based on CH50 levels which were self-administered.

- Results of the EORTC-30 quality of life instrument are shown in Figure 4 and show an improvement at the end of the trial for all four patients. The fifth patient had incomplete quality of life data, as he was withdrawn from the trial due to a suspected commodity.

- Immunogenicity was analysed, all 5 patients developed low titre antibodies but no neutralising antibodies were observed.

- The objective was to enrol additional patients in this Phase 2 trial using a revised dosage plan. Patients A, B, C and D were self-administered at 900 mg by subcutaneous injection by patients is well established.

- To answer the clinical question of whether Coversin administration improves global health status, the EORTC-30 quality of life instrument, which was self-administered, all 5 patients developed low titre antibodies but no neutralising antibodies were observed.

Fig 1, left: Terminal complement activity monitored by MicroLog CH50 ELISA for the 4 PNH patients who remained in the Phase 2 trial. Fig 1, right: Detail onset CH50 inhibition

Fig 2, left: LDH plotted as a multiple of ULN for the 4 patients who remained in the Phase 2 trial and as the mean of multiple ULN. Figure 2, right: AST over the same period

Fig 3, left: Number of units of packed red blood cells (PRBC) transfused to patients prior to and during the 90 day trial. Fig 3, right: Haemoglobin levels for 4 patients in trial

Fig 4: EORTC-30 scores at all patients

Note: The patient data is from the EORTC-30 which will be audited at the end of the Phase 2 trial. The EORTC-30 is a QOL and immunogenicity data which is from UCL central lab.