2 SYNOPSIS

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<tr><td>Name of Sponsor/Company:
Akari Therapeutics Plc</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

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<tr><td>Name of Finished Product:</td></tr>
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<tr><td colspan="3">Title of Study:
COBALT: Coversin Global Study: An Open-Label, Safety and Efficacy Trial in Paroxysmal Nocturnal Haemoglobinuria Patients</td></tr>
<tr><td colspan="3">Investigators:
▪ Dr Anita Hill (co-ordinating investigator), St James's University Hospital, United Kingdom.
▪ Dr A Kulasekararaj, King's College Hospital, United Kingdom.
▪ Prof J Windyga, Instytut Hematologii i Transfuzjologii, Poland.
▪ Prof A Hellmann, Uniwersyteckie Centrum Kliniczne Klinika Hematologii i Transplantologii, Poland
▪ Prof T Robak, Oddzial Hematologii z Pododdzialem Chemioterapii Wojewodzkiego Wielospecjalistycznego Centrum Onkologii i Traumatologii, Poland</td></tr>
<tr><td colspan="3">Study centre(s):
Two centres in the United Kingdom and three in Poland:

▪ St James's University Hospital, Leeds, United Kingdom.
▪ King's College Hospital, London, United Kingdom.
▪ Instytut Hematologii i Transfuzjologii, Warszawa, Poland.
▪ Uniwersyteckie Centrum Kliniczne Klinika Hematologii i Transplantologii, Gdansk, Poland.
▪ Oddzial Hematologii z Pododdzialem Chemioterapii Wojewodzkiego Wielospecjalistycznego Centrum Onkologii i Traumatologii, Lodz, Poland.</td></tr>
<tr><td colspan="3">Publication (reference):
None</td></tr>
<tr><td colspan="2">Studied period:

13th December 2016 (first patient enrolled) - 21st December 2017 (last patient completed)</td><td>Phase of development:

II</td></tr>
<tr><td colspan="3">Objectives:
Primary - Safety of Coversin
Secondary - Determination of effective dose and frequency of dosing for the treatment of PNH.</td></tr>
<tr><td colspan="3">Methodology:</td></tr>
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The trial was a 90-day open-label, non-comparative study in up to 10 patients with newly diagnosed PNH who had not received eculizumab (*Soliris*®) within 3 months of entry, or any other drug acting directly on the complement system. Following ablation, the trial consisted of two phases:

- an Initiation Phase, during which the patient was stabilised on treatment with Coversin administered 12-hourly.
- a Maintenance Phase, during which the patient was treated with Coversin administered 24-hourly.

Day 90 was considered to be the end of the trial. The trial was scheduled to last 90 days in total for all patients, although the exact length of each phase was adjusted to ensure that optimal laboratory and clinical support was available during the change from every 12 hours to every 24 hours dosing.

After Day 90, patients had the option to continue with Coversin treatment as part of a long-term safety maintenance study (Study AK581). Coversin could be provided through this mechanism until approval and local reimbursement.

Number of patients (planned and analysed):
- Up to 10 patients were planned to be enrolled into this study
- 8 patients were enrolled
- 8 patients were analysed

Diagnosis and main criteria for inclusion:
- Patients with a diagnosis of PNH confirmed by flow cytometry who, in the opinion of the Investigator, would benefit from treatment with a complement C5 inhibitor.
- Aged 18 and above. No upper age limit.
- Body weight ≥50 kg.

Test product, dose and mode of administration, batch number:
Coversin (rVA576) powder for solution for s.c. injection (30 mg/mL), labelled batches B3006430 (nude vials B3005187), B3006976 (B3006352), B3008315 (B3008144), B3007242 & B3007673 (B3006975), and B3008064 (B3007884) were used in this trial.

The first five patients entered this study under Protocol Version 3, which used the following Coversin dosing regimen:

Ablating Dose:	60 mg, then 3 x 30 mg every 12 hours for 2 days
Initiation Phase:	15 mg every 12 hours for 26 days (Days 3 - 28)
Maintenance Phase:	30 mg every 24 hours from Days 29 - 90

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The last three patients entered this study under Protocol Version 4, which used the following revised Coversin dosing regimen:

Ablating Dose:	60 mg then 30 mg 12 hours later
Initiation Phase:	22.5 mg every 12 hours for 27 days (Days 2 - 28)
Maintenance Phase:	45 mg every 24 hours from Days 29 - 90

Under both of the above Coversin dosing regimens adjustments to the dose were allowed, based on the response of the patient.

Duration of treatment:
90 days.

Reference therapy, dose and mode of administration, batch number:
There was no reference therapy.

Criteria for evaluation:
Efficacy:
Primary - Reduction in serum LDH to ≤ 1.8 times the ULN (*or 500 IU/L, whichever was the lower**) from Day 1 (pre-dose) to Day 29.
** Note: It became apparent that the absolute LDH 500 IU/L value was not a meaningful endpoint since the upper limit of normal for LDH varied widely from site to site (in this study from 220 to 480 IU/L). The primary analysis therefore only looked at the reduction to ≤ 1.8 times the ULN.*

Safety:
Primary - Frequency, type and relationship of AEs and Serious Adverse Events (SAEs) to treatment.

Statistical Methods:
Statistical analyses were performed using SAS® (Version 9.3 or later).

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) were used to summarise the continuous efficacy and safety data. Discrete measures were summarised using count and percentage. Unless otherwise stated, descriptive statistics showing the mean or median were displayed to one decimal place more than the original data; the standard deviation was displayed to two decimal places more than the original data; minimum and maximum were displayed to the same number of decimal places as the original data.

Given the small number of patients recruited into this trial, any significance tests or confidence intervals were purely descriptive.

SUMMARY – CONCLUSIONS

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EFFICACY RESULTS:
The primary efficacy endpoint of the trial was a reduction in serum LDH to ≤ 1.8 times the upper limit of normal (ULN) by Day 29. There was a drop in LDH over time, with median LDH ≤ 1.8 x ULN reached by Day 29 and maintained throughout the remainder of the study. The primary efficacy end point defined as the number and percentage of patients who exhibit a reduction in serum LDH ≤ 1.8 times the ULN by Day 29 was successfully met by five of the eight patients (62.5%) in the trial.

An amendment to the protocol revised the dosing for the last three patients on the basis of pharmacokinetic (PK) and pharmacodynamic ((PD) including LDH) observations from the first five patients recruited into the study. Although patient numbers are too small to make a firm conclusion, the data suggest that the revised dosing regimen improved the rate of reduction in LDH and maintained LDH at a lower level for the remainder of the study.

A total of 62.5% of patients exhibited an LDH reduction to less than 50% of the baseline value by Day 29.

All patients had a rapid reduction in CH50 to ≤ 8 U Eq/mL within 36 hours after the first dose and remained at or below that level throughout the remainder of the study up to Day 90.

Haemoglobin (Hb) levels remained steady throughout the treatment period. There was no obvious trend either up or down throughout the treatment period. On Day 1 mean Hb started at approximately 0.8x the LLN and remained at a mean of 0.8x the LLN throughout the trial.

Six patients received transfusions for PNH prior to study start, which was reduced to three patients during the three-month treatment period.

Quality of life assessments (EORTC QLQ-C30 and EQ-5D-5L) showed a general improvement in most aspects considered (global health status, & functional scales of the EORTC QLQ-C30, and all five scales (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) of the EQ-5D-5L), compared with baseline.

SAFETY RESULTS:
Overall, Coversin was well tolerated in this study. There were no drug related SAEs and few drug related AEs other than mild to moderate injection site reactions.

Treatment emergent adverse events (TEAEs) were reported in 7 (87.5%) out of the 8 patients in this study. Coversin-related TEAEs were reported in 6 (75.0%) patients, the majority of these were mild to moderate injection site reactions.

Treatment emergent serious adverse events (TE SAEs) were reported in 2 (25.0%) patients. One patient had an SAE of staphylococcal infection, and another patient had SAEs of angina

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pectoris, lethargy and dyspnoea. All four SAEs resolved during the study and were considered to be not related to Coversin.

There were no TEAEs leading to death or discontinuation from the study, and there were no life-threatening events.

The two SAEs of staphylococcal infection and angina pectoris were graded as severe. All other TEAEs were either mild or moderate.

The most frequently reported Coversin-related TEAEs were related to injection site reactions with erythema, pruritis, pain and bruising being reported in more than one patient. There were no other Coversin-related TEAEs reported in more than one patient.

Anti-Coversin antibodies were first detected in two patients at the Day 14 assessment. By the time the Day 90 assessment was reached, all patients were either positive or borderline positive for anti-Coversin antibodies. However, there was no evidence from the efficacy or PK data that the clinical response in these patients was decreasing over time, indicating that the antibodies were likely non-neutralising.

CONCLUSION:
In conclusion, in this trial Coversin was well tolerated and showed a positive safety profile and clinical response. The primary efficacy endpoint of the trial was a reduction in serum LDH to ≤ 1.8 times the upper limit of normal (ULN) by Day 29. There was a drop in LDH over time, with median LDH ≤ 1.8 x ULN reached by Day 29 and maintained throughout the remainder of the study. The primary efficacy end point defined as the number and percentage of patients who exhibit a reduction in serum LDH ≤ 1.8 times the ULN by Day 29 was successfully met by five of the eight patients (62.5%) in the trial.

The revised dosing regimen applied to the last three patients resulted in a more rapid reduction in LDH to lower levels than for the earlier patients and will be used in future clinical trials.

Date of the report:
20th December 2018