2 SYNOPSIS

Name of Sponsor/Company: Akari Therapeutics Plc	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Nomacopan		
Name of Active Ingredient: Nomacopan, rVA576 (also known as coversin, OmCI or rEV576)		

Title of Study:
CONSERVE: Coversin Long Term Safety and Efficacy Surveillance Study.

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Publication (reference):
N/A

Studied period: 14th March 2017 (1st patient, 1st dose). 1st October 2020 (last patient, last visit).	Phase of development: III

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Objectives:

Primary Objective: To provide a database of information regarding long-term administration of rVA576 (Coversin), to examine whether the drug remained safe for long periods and was acceptable to patients and that the therapeutic effect observed in the parent clinical trials was maintained.

The specific objectives of the study were:

- To observe the long term safety and efficacy of rVA576 (Coversin) in a period exceeding the 3, 6, 9 or 24 months of treatment in the parent trials.
- To assess the long term patient acceptability of rVA576 (Coversin) using the EORTC QLQ-C30 (for some PNH only), EQ-5D-5L & FACIT-F (both PNH & aHUS) instruments and the Sponsor non validated questionnaire.
- To observe the changes, if any, in the production of anti-drug antibodies (ADA) and whether such antibodies were, or became, neutralizing.

Methodology:
Open-label, non-comparative.

Patients who could participate in this trial were those with diseases requiring complement inhibition who had previously been in Akari clinical trials and who wished to continue to receive rVA576 after their active participation in the trial had terminated, and also patients treated under compassionate use or named patient arrangements who wished to continue on rVA576 therapy.

Number of patients (planned and analysed):

Planned: Approximately 50 patients.

Analysed: 15 PNH patients (the study was terminated early because the Sponsor closed their global Phase III PNH programme). No aHUS patients were recruited.

Diagnosis and main criteria for inclusion:

- Patients 18 years and above treated with rVA576 under other Akari clinical trial protocols and wished to remain on rVA576 at the conclusion of that trial.
- In the opinion of the treating responsible physician, the patient was receiving clinical benefit from continued treatment with the study drug.
- Evidence of sustained complement inhibition by CH50 assay.
- Patients with evidence of an active meningococcal infection were not allowed to enter this trial.
- Weight > 50 kg.
- Received appropriate prophylaxis against *Neisseria meningitidis* infection, by both immunisation and continuous or intermittent antibiotics.

Test product, dose and mode of administration:
Coversin (nomacopan, rVA576) powder for solution for subcutaneous injection (30 mg/mL).

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Patients entering this trial would initially receive the same dose of rVA576 as they were receiving at the end of their previous trial. If a change in dose or dose frequency of rVA576 became desirable, the responsible physician had discretion to alter the treatment regime in consultation with the Sponsor's medical representative. During any such changes careful monitoring of complement inhibition was mandatory, which included regular assessment of serum LDH and CH50 as well as the patient's clinical status.

In the event of an increase of dose or dose frequency, an ablating dose could be given to ensure complete complement inhibition before the new dose was started. It was assumed that a reduction of dose or dose frequency was only considered if the patient's prior complement control was adequate and hence no ablating phase dose needed to be given before starting the new dose.

The ablating phase dose consisted of four doses; an initial dose of 60 mg followed by three doses of 30 mg every 12 hours over two days. Doses could be adjusted throughout the study depending on patient response.

Duration of treatment:
Up to four years planned.

Patients for whom rVA576 was found to be effective in this clinical trial and who wished to continue on the drug following conclusion of this trial, could continue to receive rVA576, subject to approval of the applicable governmental agency, until rVA576 receives marketing approval, or the trial was terminated.

Reference therapy, dose and mode of administration, batch number:
Not applicable.

Criteria for evaluation:
Primary Endpoint
The long- term safety of rVA576 (Coversin) therapy as assessed by AEs, serious adverse events (SAEs), vital signs, and results of standard laboratory tests (clinical chemistry, haematology, urinalysis) and results of electrocardiograms (ECGs).

Statistical Methods:
As this was a long-term safety study, all data presented is descriptive in nature.
Due to the early termination of this study, only a subset of the outputs planned were produced.

Summary - Conclusions
A total of 15 patients were enrolled into this study from four parent studies. Seven patients came from study AK579 (Phase II safety and efficacy study in PNH), six from study AK580

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(Phase III safety and efficacy study in PNH), and one each from studies AK585 (Phase II study in PNH patients with resistance to eculizumab) and AK578 (also a Phase II study in PNH patients with resistance to eculizumab).

In this long-term safety study, patients were exposed to study drugs for a median 567 days (range 88 - 1184). The study was terminated early because the Sponsor closed their global Phase III PNH programme. Overall, rVA576 was well tolerated.

During the entire study period, 11 out of 15 patients (73%) had no PRBC transfusions. Two of the 15 patients were transfusion independent prior to receiving nomacopan and both patients remained transfusion independent during the study. Of the 13 patients who were transfusion dependent prior to starting this study, nine (69%) had no PRBC transfusions during the entire AK581 study period.

There was no obvious change in LDH (increase or decrease) during treatment compared to the LDH levels observed in the parent trials where subjects were also receiving rVA576. The terminal complement activity (as measured by CH50) remained below the lower limit of quantification in all subjects (n = 124 measurements) throughout treatment with just two exceptions (patients 616-101-002 and 616-102-001 who had a CH50 U Eq/mL values of 13.8 and 11.6 on Days 224 and 245 of the trial respectively).

PK analysis showed a stable level of unbound rVA576 during the treatment period for all patients which supports good patient compliance with dosing and self-administration.

The most frequently reported TEAEs were infection related with 11 of the 15 patients reporting infections (predominantly urinary and respiratory tract infections, bronchitis and nasopharyngitis). A total of 13 SAEs were reported in three patients, only one of which (urinary tract infection at Day 274 in patient 032-101-001) was considered to be possibly related to study drug, the remainder were considered unrelated. There were no deaths during the study, and no AEs that resulted in any change to the administration of study drug.

There was nothing of concern reported for vital signs, ECG, or physical examination.

There were no thrombotic or Major Adverse Vascular Events (MAVEs) reported during the entire period of the study. Haemolytic events were observed in four patients whilst on treatment. They comprised an exacerbation of haemolytic anaemia which occurred on Day 56 (patient 440-101-002, ongoing at the end of study, Day 250), and Day 170 (patient 440-101-001, resolved 15 days later), and blood in the urine on Day 31 (patient 144-103-001,

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coincident with low RBC and haemoglobin) and Day 283 (patient 032-101-001, coincident with a urinary tract infection).

In conclusion, rVA576 was well tolerated in this group of patients, and 73% (11/15) of the patients had no PRBC transfusions during this long-term study. Avoidance of PRBC transfusion and absence of life-threatening MAVE are the clinical outcomes of most concern to clinicians treating PNH.

Date of the report:
30th April 2021