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:
CAPSTONE: Phase III Confirmatory Assessment Protocol: rVA576 Safety and Efficacy in Three-Part, Two-Arm, Randomised Open Label Evaluation in Patients with Paroxysmal Nocturnal Haemoglobinuria.

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Publication (reference):
N/A

Studied period: 10th July 2018 (1st patient Day 1). 2nd September 2020 (Last patient completed).	Phase of development: III

Objectives:

Primary Objective: To demonstrate the efficacy of rVA576 plus standard of care (SoC) compared to SoC in patients with uncontrolled haemolysis due to paroxysmal nocturnal haemoglobinuria (PNH).

Secondary Objective: To assess the safety and tolerability of rVA576 in treatment of patients with PNH.

Methodology:
This was a three-part, two-arm, randomised, open label study.

Part 1 - An up to 3-month observation period in which patients were treated with SoC. All patients recruited to Part 1 of the trial had had at least 4 transfusion events in the 12 months prior to screening. During Part 1, the patients could receive a qualifying transfusion of packed red blood cells (PRBC) that permitted entry into Part 2 of the trial if their haemoglobin (Hb) fell below 90 g/L with PNH symptoms or below 70 g/L with or without symptoms. Patients who did not require a qualifying transfusion by the end of the observation period were to leave the trial (withdrawn patients) and were not permitted to be re-screened.

Patients who received a qualifying transfusion had the Hb value, which triggered their requirement for a transfusion, used as their set point which mandated the Hb level at which further transfusions were to take place. If the Hb value was less than 70 g/L at trigger for qualifying transfusion, the set point mandating further transfusions was set to 70 g/L. Patients were to receive their qualifying transfusion based on a pre-determined transfusion algorithm (see below and Section 9.2) within a maximum of 48 hours of the Hb value which triggered the clinical decision to transfuse.

Part 2: - A 6-month treatment period where patients were randomised to either rVA576 plus SoC (Arm 1) or SoC (Arm 2). Following receipt of the qualifying transfusion in Part 1, patients were to move into Part 2 within 1 - 3 days to begin treatment.

At any time that a patient fell below their Hb set point during the 6-month treatment period, they were to receive an appropriate number of units of PRBCs according to a pre-determined algorithm based on prior transfusion history (see Section 9.2).

Part 3: - A 3-month maintenance period where patients in Arm 1 (rVA576 plus SoC) were to continue receiving treatment for a further 3 months, and patients in Arm 2 (SoC) were to switch from SoC only to rVA576 plus SoC for 3 months.

At any time that a patient fell below their Hb set point during the 3-month maintenance period, they were to receive an appropriate number of units of PRBCs according to a pre-determined algorithm based on prior transfusion history.

At the end of Part 3, all patients were to be offered continued treatment with rVA576 under the long-term safety study AK581 (CONSERVE), if the Investigator believed the patient was benefitting from treatment.

Follow up Visit: A safety visit was to be conducted approximately 30 days after the last study visit. This visit was applicable for patients who completed Part 3, but were not continuing into the long-term safety study, and for those patients who withdrew in Part 2. No safety follow-up was required for patients who were withdrawn in the observation period (Part 1).

Transfusion algorithm and set point:
The transfusion algorithm was patient specific and based on segmenting the patient's 12-month transfusion history prior to screening, by Hb level and quantity of PRBC or whole blood transfused. This algorithm mandated the quantity of PRBCs, to be transfused depending on which category a patient was in when a transfusion was required in Part 1:

- Hb > 80 g/L, but ≤ 90 g/L
- Hb > 70g/L, but ≤ 80g/L
- Hb ≤ 70g/L

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The minimum transfusion set point was 70 g/L. If the transfusion in the observation period (Part 1) was below 70 g/L, then the set point became 70 g/L.

Number of subjects (planned and analysed):
Planned: 30 (minimum) in Part 2
Randomised: 9 (the study was terminated early because the Sponsor closed their global Phase III PNH programme).

Diagnosis and main criteria for inclusion:

- Diagnosed with PNH confirmed by flow cytometry.
- Have not received any complement inhibitor within the 4 months prior to screening.
- ≥ 18 years of age at the time of screening.
- Weight ≥ 50 kg.
- Complete transfusion medical history for 12 months prior to entering the observation period and definitely prior to receiving the qualifying transfusion must be available to the patient's Investigator and be verifiable by the Sponsor or its representative.
- Transfusion dependent and has received at least four episodes of transfusion of whole blood or PRBC during the 12 months prior to entering the observation period (Part 1), with a minimum of four units in total, and a minimum of one unit at each transfusion episode.
- LDH ≥ 1.5 x ULN per the local lab.
- Willing to receive appropriate prophylaxis against *Neisseria meningitidis* infection, by both immunisation and continuous or intermittent antibiotics.

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

Duration of treatment:
Arm 1: Six months of treatment (rVA576 plus SoC), followed by a further three months of continued treatment with rVA576 plus SoC. A total of 9 months on rVA576 plus SoC.

Arm 2: Six months on SoC only followed by three months of treatment with rVA576 plus SoC. A total of 3 months on rVA576 plus SoC.

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

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Criteria for evaluation:

Primary Endpoint:
Hb stabilisation rate, defined as Hb greater than the set point for each patient defined during the pre-study randomisation period, and the avoidance of PRBC transfusions during the treatment period.

The primary endpoint was to be assessed at the end of Part 2.

Secondary Endpoints:
- Number of units of PRBC transfused from baseline Day 1 (start of Part 2) to Day 180.
- Percentage of patients who achieve transfusion avoidance from baseline Day 1 (start of Part 2) to Day 180.
- Change in QoL score using FACIT-F from baseline Day 1 (start of Part 2) to Day 180.
- AUC [LDH] from baseline Day 1 (start of Part 2) to Day 180.
- CH50 levels from baseline Day 1 (start of Part 2) to Day 180.

Statistical Methods:
Due to the study being terminated early with 9 of the planned 30 patients recruited, only descriptive efficacy data are presented and no formal statistical analyses undertaken. Summary safety data are presented.

Summary - Conclusions
Ten patients were enrolled into Part 1, of whom nine were randomised, four receiving rVA576 with SoC during Part 2, and five receiving SoC only during Part 2. All nine patients received rVA576 with SoC in Part 3. Due to the study being terminated early, with only 9 patients of the 30 who were planned to be recruited, only descriptive efficacy data and summary safety data are presented.

All four patients (100%) receiving rVA576 with SoC achieved transfusion independence, according to the definition used in the primary endpoint, for the six consecutive months after the initiation of treatment, compared with none of the 5 patients (0%) receiving SoC alone. In Part 2 of the study the first transfusion in the SoC arm occurred within the first 5 days of starting the study, and all five patients in the SoC arm had a first transfusion by Day 130, compared with no patients in the rVA576 plus SoC arm, who remained transfusion independent throughout

The 4 patients in the rVA576 plus SoC arm went from receiving a combined total of 21 units of PRBCs in the 180 days prior to screening, to receiving a total of 0 units in the 180 days after initiation of rVA576 treatment. By comparison, the 5 patients in the SoC arm received a combined total of 21 units in the 180 days prior to screening, and a total of 29 units in the 180 days after initiation of SoC treatment.

Patients in the SoC group in Part 2 switched to start receiving rVA576 with SoC at Day 180. A total of 18 units were received in the 90 days prior to the switch, compared with three units in the 90 days after

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the switch. None of the patients (0%) achieved transfusion independence in the 90 days prior to the switch, compared with four of the five patients (80%) in the 90 days after switching to rVA576.

The Hb level in the rVA576 with SoC group increased rapidly at the beginning of treatment and remained consistently above the SoC alone group for the first 180 days, despite the fact that the SoC group (but not rVA576 group) were receiving transfusions. The Hb levels in the SoC only group rose when these patients started receiving rVA576.

There was a dramatic difference in median LDH levels, reported as relative to the upper limit of normal (ULN), between the two treatment groups in Part 2 of the study. In the rVA576 treatment arm LDH levels rapidly decreased by ~80% from a median baseline value of 10 - 11 times the ULN to a median value of approximately 2 times the ULN by Day 14, and thereafter remained fairly stable throughout the 6-month treatment period. By contrast, the LDH levels of the SoC only treated patients did not drop and remained between a median of 8 - 11 times the ULN throughout Part 2 of the study. The LDH levels of the SoC only group dropped rapidly from Day 180 onwards when the patients started receiving rVA576.

There were no Major Adverse Vascular Events (MAVEs) observed in any patient.

Overall, rVA576 was well tolerated in this study. There were no treatment related serious adverse events (SAEs) and few treatment related AEs. Three patients (all receiving rVA576 with SoC during Part 2) had injection site events which were considered related to study drug, and two patients had events (QTc prolongation, hypercalcaemia, hypoglycaemia, hypophosphataemia, & headache) which were considered possibly related to study drug. All treatment related events reported occurred during Part 2 of the study, were mild in nature, did not result in any action in terms of changes to study drug administration, and the patients recovered. There were no treatment related events reported in Part 3.

The majority of AEs reported in this study were either mild or moderate. There was a total of four severe AEs reported in two patients. Three of these events (cholelithiasis, haemoglobinuria and catheter site infection) were classed as SAEs and resulted in hospitalisation or prolongation of hospitalisation. There was one further SAE (patient on SoC), gastroenteritis viral, which was considered mild in severity. None of the events were considered related to study drug by the Investigators.

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

There were no changes of note to any laboratory parameters, vital signs, ECG or physical findings.

In conclusion, rVA576 was well tolerated in this group of patients with PNH. The limited descriptive efficacy data also strongly suggest that rVA576 had a marked effect on reducing transfusion requirements (the clinical marker of most significance to treating clinicians), stabilising Hb levels and greatly reducing LDH levels.

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