SYNOPSIS ***ANNEX I***

Name of Sponsor/Company: **Arctic Therapeutics, Ehf**	Individual Study Table Referring to Part of the Dossier Volume:	*(For National Authority Use only)*
Name of Finished Product: **AT-1**		
Name of Active Ingredient: **N-acetyl cystein (NAC)**	Page:	

Title of Study:
Phase IIa biomarker study to evaluate the efficacy, safety, and tolerability of AT-1 in patients with hereditary cystatin C amyloid angiopathy (HCAA) - the AT1-HCCAA study

Investigators:
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Study centre(s):
Landspítali University Hospital, Reykjavík

Publication (reference):
N/A

Studied period (years): 1.5yrs First subject enrolled: July 1, 2019 Last subject completed: Sept 3, 2020	Phase of development: **Phase II**

Objectives:
Evaluation of efficacy, safety, and tolerabilty of oral AT-1 in patients with HCCAA

Methodology:
Oral daily administration of drug daily for 9 month; evaluation at 3, 6, and 9 months for skin and blood biomarkers and cognitive status using dementia rating scales.

Number of patients (planned and analysed):
50 subjects planned; 22 subjects screened; 17 subjects enrolled; 16 subjects completed and analyzed

Diagnosis and main criteria for inclusion:
Subject is carrier for L68Q mutation in Cystatin C that causes Hereditary Cystatin C Amyloid Angiopathy (HCAA); subject may or may not be showing overt symptoms of HCCAA such as dementia

Test product, dose and mode of administration, batch number: **600mg effervescent tablet of NAC (AT-1)**
2 tablets (1200mg) of AT-1 administered orally (*per os*) 2x a day (bid)
Sandoz batch number: IS/1/15/102/01

Duration of treatment: 16 of 17 subjects dosed for max duration of 9 months

Reference therapy, dose and mode of administration, batch number:
N/A: All subjects dosed with AT-1 test product only

***ANNEX 1** cont.*

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Name of Finished Product: **AT-1**		
Name of Active Ingredient: **N-acetyl cystein (NAC)**		

Criteria for evaluation:

Efficacy: 1º Endpoints- Change/stabilization of: 1) skin deposition of Cystatin C (CC)/amyloid aggregates assessed by skin biopsy, and 2) Cognitive status assessed by dementia rating scale, following 3, 6, 9 mo treatment w/ AT-1.

2º Endpoints- 1) Pharmacokinetic (PK)parameters of AT-1 in blood from 5 subjects; 2) oxidized vs. reduced glutathione levels in blood; 3) CC/amyloid complexes in blood; 4) CC levels in urine. Substrates measured in 2)-4) assessed at 3, 6, and 9 mo following treatment w/ AT-1.

Safety: Adverse event (AE) reporting using MedDRA codes and tabulated by System Organ Class and Preferred Term; Reporting of laboratory values outside normal limits.

Statistical methods: Analysis of biomarker staining of CC/amyloid deposits in skin using ANOVA model and fixed effect for dose level, age group, and dose level by age group interactions. Quantitative variables from dementia rating scales are summarized using descriptive statistics, continuous variables are presented as N, mean and/or median, standard deviaton, and range, while categorical variables are presented using frequencies and percentage. PK parameters including C_{max}, T_{max}, and $T_{1/2}$ are calculated and compared with previously reported values using ANOVA model.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS

1) Reduction of CC/amyloid deposits in skin observed in all time points (3, 6, and 9 mo) in all 16 patients who completed study
2) No serious bleeds observed in all subjects for duration of study, which is significantly less than natural history of disease; notably, one subject who experienced 3 serious bleeds prior to study had one minor bleed during study and follow up (5 years)
3) No deterioration in cognitive status for duration of study in all enrolled subjects
4) Other cell activation markers in skin showed reduction at 9 months following AT-1 treatment
5) Significant reduction in high molecular weight CC complexes in blood following treatment (p = ?, N = ?) at all time points?
6) CC levels in urine: assay under development
7) Oxidized vs. reduced glutatione levels in blood: assay under development
8) PK parameters: analysis pending

SAFETY RESULTS:

1) Eight (8): serious adverse events (SAE's) observed: 5 self-resolving bleed; one incidence of migraine that likely manifested from another self-resolving bleed; 2 pregnancies. The observations made by the research staff suggest that the incidence of bleeds were less severe and frequent compared to natural history of disease, and subjects who experienced pregnancy during study had difficulty conceiving prior to study, therefore effect of study drug cannot be entirely excluded.
2) No other notable AEs or abnormal laboratory measures observed.
3) Two (2) enrolled subjects discontinued study due to pregnancy.

CONCLUSION:

1) AT-1 was safe and well tolerated in all subjects
2) AT-1 treatment significantly reduced CC/amyloid deposits and complexes as measured in skin and blood; these deposits and complexes are considered the pathological agent leading to severe events in HCCAA
3) AT-1 treatment appears to prevent the incidence of severe events and associated deterioration in cognitive function in HCCAA affected subjects and L68Q carriers compared that expected based on natural history of disease.

Date of the report: 9/2/2021