November 30, 2022

FOCUS-C9 Clinical Trial Advances; Complete Data Due 1st Half 2023

The ongoing trial is investigating effects of Wave Life Sciences' WVE-004

The ongoing clinical trial of Wave Life Sciences' WVE-004 in people with ALS and FTD associated with *C9orf72* gene mutations has been expanded to evaluate a quarterly dose of the medication.

The decision to administer WVE-004 every three months was based on the potency and durability of effects with other dosing regimens. Data from all groups in the Phase 1b/2a FOCUS-C9 trial (NCT04931862) are expected in the first half of 2023, Wave said in a company press release announcing its financial results and business updates.

An open-label extension study also was initiated for those who complete the FOCUS-C9 trial.

C9orf72 gene mutations are one of the most common genetic causes of ALS and FTD. Normally, this gene has a region where six "letters" of the genetic code (GGGGCC) are repeated a few dozen times. But ALS and FTD-associated mutations expand these repeats to a few hundreds or thousands, resulting in abnormal proteins that are prone to forming toxic clumps inside cells.

WVE-004 was designed to reduce these toxic proteins' production by interfering with the gene's messenger RNA (mRNA), an intermediary molecule the gene produces as a template for making the resulting protein.

Experiments in animal models have shown the medication can potently reduce the toxic RNA molecules and small proteins associated with *C9orf72* mutations, while preserving healthy C9orf72 protein production in the brain and spinal cord.

Wave launched FOCUS-C9 last year to evaluate the safety and pharmacological properties of WVE-004 in people with ALS and/or FTD associated with *C9orf72* mutations. In the trial's first part, participants received a single dose of WVE-004 or a placebo via injection through the spine (intrathecal injection).

Initial data — including from two patients on a 10 mg dose of WVE-004, four on a 30 mg dose, three on a 60 mg dose, and three on a placebo — showed the medication reduced poly(GP) levels across all active treatment groups.

Poly(GP) is one of the toxic proteins produced from the repeat expansion region in *C9orf72* and a key biomarker of ALS and FTD associated with mutations in this gene. At 85 days after treatment, patients on the 30 mg dose showed significant reductions in poly(GP) — as much as 34% compared with the placebo group.

Since poly(GP) was still declining during the analysis, the company extended the observation period from three to six months to identify the maximum reduction and the duration of effects after a single dose.

FOCUS-C9 was also adapted to include additional patients on the 20 mg and 30 mg single dose groups, based on the durability and potency observed in this group.

To date, the frequency of side effects has been similar across WVE-004 and placebo groups, most being mild to moderate in intensity. Four participants, including one on a placebo, had severe or serious side effects, but only one was deemed related to WVE-004.

In Phase 2a, participants are receiving multiple doses of WVE-004. Six will be given a 10 mg dose each month for four months and the trial has been expanded to evaluate every three-month dosing of 10 and 20 mg doses, 10 patients in each group.

Source: **ALS News Today**

FOCUS-C9 recruits at the following locations in Europe:

Belgium

UZ Leuven
Leuven, Belgium, 3000
Contact: Rik Vandenberghe, MD, PhD 016344280 rik.vandenberghe@uz.kuleuven.ac.be
Principal Investigator: Rick Vandenberghe, MD, PhD

Ireland

St James Hospital - Ireland
Dublin, Ireland, D08 NHY1
Principal Investigator: Orla Hardiman, BSc MB BCh BAO MD FRCPI FAAN

Netherlands

Erasmus University MC
Rotterdam, Netherlands, 3015
Principal Investigator: Harro Seelar, MD, PhD, MSc

Universitair Medisch Centrum Utrecht
Utrecht, Netherlands
Principal Investigator: Leonard van den Berg, MD, PhD

Sweden

Karolinska University Hospital
Solna, Sweden
Principal Investigator: Anne B Hanson, MD, PhD

United Kingdom

University of Cambridge
Cambridge, United Kingdom
Principal Investigator: James Rowe, MD, PhD

University College London Hospital
London, United Kingdom, WC1N 3BG
Principal Investigator: Jonathan Rohrer, MD, PhD

King's College Hospital
London, United Kingdom, WC2R 2LS
Principal Investigator: Christopher Shaw, MD, FRACP

University of Oxford - Nuffield Department of Clinical Neurosciences
Oxford, United Kingdom, OX3 7LF
Principal Investigator: Kevin Talbot, MB BS, DPhil, FRCP

University of Sheffield
Sheffield, United Kingdom, S10 2TN
Contact: Jonathan Cooper-Knock, MD, PhD j.cooper-knock@sheffield.ac.uk
Principal Investigator: Jonathan Cooper-Knock, MD, PhD