

# Clinical Trial Highlights: Phase 3 in Focus – Ampreloxetine, Theravance Biopharma

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The phase 3 in focus for this issue is ampreloxetine, also known as TD9855, under development for the symptomatic treatment of neurogenic orthostatic hypertension (nOH) by Theravance Biopharma.

## Background:

Autonomic dysfunction is a common problem for people with Parkinson's (PwP). One manifestation of this is nOH, a sustained fall in blood pressure upon standing. This can lead to dizziness and even fainting, the consequences of which can be quite severe, and affects one in three PwP during the course of disease progression. nOH can also be associated with supine hypertension, thereby complicating pharmacological treatment options [1].

Current treatments for nOH include fludrocortisone, pyridostigmine, midodrine (a direct  $\alpha_1$ -adrenoreceptor agonist), and droxidopa (a norepinephrine precursor). Droxidopa is the only drug that has FDA approved indication for nOH. None of the options fully meets the clinical need. There is a lack of response in a subset of patients, no durable effects, limiting safety profiles and multiple daily dosing [2]. This presents the opportunity for the once daily dosing option presented by ampreloxetine, a norepinephrine reuptake inhibitor. This mechanism of action prolongs the effect of endogenous norepinephrine.

Ampreloxetine has been through a successful phase 2 study (NCT02705755) demonstrating proof of concept. There are three phase 3 trials in progress. The first, SEQUOIA, is a four-week randomized, placebo-controlled, double-blind parallel group design. Participants who, in the opinion of the investigator, will benefit from continued treatment with ampreloxetine, will then move on to the REDWOOD study, which lasts for 22 weeks and includes a six-week randomized withdrawal. Those patients that complete REDWOOD can then move onto an open label safety and tolerability study named OAK, lasting for three years. These phase 3 studies are reviewed below. In parallel, Theravance Biopharma are also conducting a phase 1 pharmacokinetic study in people with hepatic impairment (NCT04200573).

## SEQUOIA phase 3

**Title:** A phase 3, 4-week, multicentre (130 locations), randomized, double-blind, placebo-controlled, parallel-group study of TD-9855 in treating symptomatic neurogenic orthostatic hypotension in subjects with primary autonomic failure.

## Phase: 3

**Objective:** To evaluate the efficacy, safety, and tolerability of ampreloxetine (TD-9855) in subjects with primary autonomic failures [Multiple System Atrophy (MSA), Parkinson's disease (PD), or Primary Autonomic Failure (PAF)] and symptomatic nOH.

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**Status:** Recruiting.

**Clinicaltrials.gov ID:** NCT03750552

**Sponsor:** Theravance Biopharma

**Estimated Enrolment:** 188 participants

**Estimated Completion Date:** August 2021

**Study Design:** Participants will be randomized to receive a single oral daily dose of amprelosetine or placebo. Blinding will be for the investigator, participant, care provider and outcome assessor. There are three phases, a four-week screening, four weeks of randomized treatment and a two week follow up. Apart from the screening visit, the required visits can be conducted either in clinic or remotely.

**Outcome Measures:** The primary outcome measure is the change from baseline in Orthostatic Hypotension Symptom Assessment (OHSA) question #1 at week 4. Question #1 assesses dizziness, light-headedness, feeling faint, or feeling like you might blackout. The timeframe is baseline to week 4.

The secondary outcome measures are:

1. Change from baseline in OHSA composite score in weeks 1 to 4 (timeframe: baseline, week 1, week 2, week 3, week 4)

2. Change from baseline in Orthostatic Hypotension Daily Activities Scale (OHDAS) composite score in weeks 1 to 4 (timeframe: baseline, week 1, week 2, week 3, week 4). OHDAS is an assessment of how low blood pressure symptoms affect daily life.

3. Using the Patient Global Impression of Change (PGI-C) scale, a subject rates their total improvement at week 4 compared to baseline.

4. Incidence of patient-reported falls at week 4.

### REDWOOD phase 3

**Title:** A phase 3, 22-week, multi-center (61 locations), randomized withdrawal study of TD-9855 in treating symptomatic neurogenic orthostatic hypotension in subjects with primary autonomic failure

**Phase:** 3

**Objective:** To evaluate the sustained benefit in efficacy and safety of amprelosetine in subjects with primary autonomic failures (MSA, PD, or PAF) and symptomatic nOH.

**Status:** Recruiting.

**Clinicaltrials.gov ID:** NCT03829657

**Sponsor:** Theravance Biopharma

**Estimated Enrolment:** 258 participants

**Estimated Completion Date:** August 2022

**Study Design:** REDWOOD consists of three phases. It starts with 16 weeks of open-label (OL) treatment, then a six-week randomized placebo-

controlled treatment phase, and finally a two-week follow-up which is only for patients who do not enroll in OAK, a long-term extension safety study. The blinding for the second phase is quadruple (participant, care provider, investigator, and outcomes assessor).

Participants in the SEQUOIA study are eligible to enter REDWOOD. In addition, the trial is recruiting *de novo* patients.

**Outcome Measures:** The primary outcome measure is the change from baseline in the OHSA question #1 score of one point and worsening of disease severity as assessed by a one-point change in Patient Global Impression of Severity (PGI-S) at week six post randomisation (week 16 to week 22).

The secondary outcome measures, all assessed at week six post-randomization (week 16 to week 22), are:

1. Change from baseline in OHSA#1.

2. Change from baseline in OHSA composite score.

3. Change from baseline in OHDAS composite score.

4. Change from baseline in PGI-S.

5. Change from baseline in percent of time spent in standing position as measured by a wearable device that provides date- and time-stamped activity information to measure the time spent in supine, sitting, and standing positions.

6. Change from baseline in average number of steps taken as measured by a wearable device.

### OAK phase 3

**Title:** A phase 3, 182-week, open-label, multi-center (26 locations) extension study to investigate the safety and tolerability of TD-9855 in treating symptomatic neurogenic orthostatic hypotension (nOH) in subjects with primary autonomic failure.

**Phase:** 3

**Objective:** To evaluate the safety and tolerability of amprelosetine in subjects with primary autonomic failure (MSA, PD, and PAF) and symptomatic nOH.

**Status:** Recruiting.

**Clinicaltrials.gov ID:** NCT04095793

**Sponsor:** Theravance Biopharma

**Estimated Enrolment:** 120 participants

**Estimated Completion Date:** December 2025

**Study Design:** OAK has three phases, all open label. The first is a 26-week treatment phase, followed by a 156-week treatment extension and ending with a two-week follow up. The study is only open to those participants who complete the REDWOOD trial.

**Outcome Measures:** There are 10 primary outcome measures and no secondary ones, all compared to baseline at week 26:

1. Physical examination - number of subjects with new abnormalities.

2. Neurological examination - number of subjects with new abnormalities.

3. Vital Signs - number of subjects with clinically significant vital sign abnormalities.

4. ECG - number of subjects with clinically significant ECG findings.

5. Clinical laboratory tests - number of subjects with laboratory test abnormalities.

6. Changes in concomitant medications.

7. Adverse events (AEs) - incidence and severity of treatment-emergent adverse events.

8. Subject compliance to study treatment - number of subjects determined to be compliant with study medications.

9. Changes in incidence of falls.

10. Changes from baseline in Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) and will be used for all visits.

**Comments:**

Participants in the series of amprelosetine trials are being recruited in two pathways. The first is SEQUOIA followed by REDWOOD and finishing with OAK. The second is REDWOOD followed by OAK. There will, of course, be dropouts along the

way. The inclusion criteria require subjects over the age of 30, diagnosed with nOH and one of PD, MSA or PAF. These criteria are also used to assess *de novo* entrants to REDWOOD. Exclusion criteria prevent the use of any monoamine oxidase inhibitor (MAOI), which is notable given that MAOI-B inhibitors are very commonly used in PD. Participants in OAK can only come from the REDWOOD trial and must continue to meet the latter's inclusion criteria.

The slightly unusual design of REDWOOD is intended to measure the durability of action of amprelosetine. Participants are established on active dose for 16 weeks, prior to the six-week blinded phase to assess amprelosetine against placebo. All of the outcome measures are focused on this phase.

Given the scale of the problem with nOH in PD, with a reduced quality of life, and the potential for serious injury from falls, we look forward to the release of data from the SEQUOIA trial shortly after the projected completion date of August 2021.

## REFERENCES

- [1] Fanciulli, Alessandra; Leys, Fabian; Falup-Pecurariu, Cristian; Thijs, Roland; Wenning, Gregor K (2020) Management of Orthostatic Hypotension in Parkinson's Disease. *J Parkinson Dis* **10** pp. S57-S64.
- [2] Theravance Biopharma: Fourth Quarter and Full Year 2020 Financial Results and Business Update. <https://investor.theravance.com/static-files/72bfc141-5fef-4d1b-bf33-19ef0d12ff5b>. Last updated February 23, 2021. Accessed February 28, 2021.