NORDVALE
THERAPEUTICS

PROTOCOL NVT-AD-3001

Statistical Analysis Plan

NVT-AD-3001: a 24-week, randomised, double-blind, placebo-controlled study of xanomeline transdermal therapeutic system in patients with mild to moderate Alzheimer's disease

COMPOUND
Xanomeline transdermal therapeutic system

INDICATION
Mild to moderate Alzheimer's disease

REPORT VERSION
1.0

STUDY PHASE
Phase 2

SPONSOR
Nordvale Therapeutics

REPORT DATE
2026-06-01

Nordvale Therapeutics is a fictional sponsor. This report is a Quarto demonstration built from the public CDISC pilot data shipped with pharmaverseadam, and is not a regulatory submission. It was built by Mickaël Canouil (github.com/mcanouil/demo-quarto-clinical-report), who is not an author of the fictional study report.

Document control

Version	Date	Summary of changes
1.0	2026-06-01	Finalised prior to database lock.

Approval

By signing this page the approvers confirm that the report describes the conduct and results of the study accurately and completely.

Study Statistician
Biostatistics

Signature Date

Clinical Study Lead
Clinical Development

Signature Date

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1 Introduction

This Statistical Analysis Plan (SAP) states the analysis populations and statistical methods for study NVT-AD-3001 prospectively, before database lock, per ICH E9 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use 1998). The Clinical Study Report (CSR) that follows database lock narrates the results of the analyses specified here; sections of the CSR methods chapter cross-reference the SAP sections below by number.

2 Study design and objectives

The study objectives and design are as stated in the protocol and summarised in the CSR's study objectives and design chapter. This SAP covers only the statistical treatment of the primary and secondary endpoints, the safety evaluation, and the analysis populations that support them.

3 Analysis populations

3.1 Intention-to-treat population

The intention-to-treat (ITT) population comprises all randomised subjects, analysed according to the treatment to which they were randomised. Since every randomised subject in this study receives at least one dose of study drug, the ITT population and the randomised population contain the same subjects. Subjects whose actual treatment differs from their planned treatment remain in the ITT population under their planned treatment.

3.2 Safety population

The safety population comprises all randomised subjects who received at least one dose of study drug, analysed according to the treatment actually received.

3.3 Per-protocol population

The per-protocol (PP) population comprises safety-population subjects who complete the study without a major protocol deviation affecting the primary endpoint. Protocol deviations are adjudicated by the study team ahead of database lock; where deviation data are unavailable, the PP population defaults to safety-population completers, which excludes subjects who discontinued for a protocol violation since they are by definition not completers.

4 Primary endpoint

4.1 Endpoint definition

The primary endpoint is the time from first dose to the first dermatologic treatment-emergent adverse event, defined as an event with a system organ class of skin and subcutaneous tissue disorders that started on or after the first dose. Subjects without such an event are censored at the last date known to be alive. The endpoint is derived from adverse event data, so it is a safety endpoint analysed with efficacy methods; it serves as the primary endpoint of this demonstration because the underlying public data carry no efficacy measure.

4.2 Statistical method

Time to event is summarised by treatment group with Kaplan-Meier estimates of the cumulative incidence, medians and two-sided 95% confidence intervals (Kaplan and Meier 1958). Treatment groups are compared with a Cox proportional hazards model with treatment as the only covariate, taking placebo as the reference group (Cox 1972). This is the primary analysis and is conducted on the ITT population.

4.3 Supportive and subgroup analyses

As a supportive analysis, the primary Cox model is repeated on the per-protocol population, to assess the sensitivity of the primary result to early discontinuation. As a further supportive analysis, the treatment effect on the primary endpoint is estimated within subgroups defined by sex and by age group (18-64, over 64), to assess consistency of the effect across those subgroups. Neither analysis is adjusted for multiplicity; both are descriptive and supportive of the primary analysis.

5 Secondary endpoint

5.1 Endpoint definition

The secondary endpoint is change from baseline in systolic blood pressure at week 24.

5.2 Statistical method

Change from baseline is analysed with an analysis of covariance model including treatment group as a factor and the baseline value as a covariate. Least-squares means, their standard errors, and two-sided 95% confidence intervals are reported for each treatment group, together with the difference from placebo. The two comparisons against placebo are not adjusted for multiplicity, since the secondary endpoint is descriptive. Blood pressure is measured in three postures, each with its own baseline; the supine measurement is used, so each subject contributes one observation. This analysis is conducted on the safety population.

6 Safety analyses

Safety analyses are descriptive and conducted on the safety population: extent of exposure; prior and concomitant medications; incidence of treatment-emergent adverse events overall, by system organ class and preferred term, by maximum severity, and by relationship to study drug; serious adverse events and deaths; shift from baseline to worst post-baseline reference-range category for selected laboratory analytes, for vital signs and for the QTcF interval; and a screen of the laboratory data against the aminotransferase and bilirubin criteria for potential drug-induced liver injury. Adverse event, concomitant medication and medical history tables report the terms reached by at least 5% of the subjects in any one treatment group. Medical history is a baseline characteristic and is summarised on the randomised population by planned treatment. No formal hypothesis tests are planned for safety endpoints.

7 Handling of missing data

No imputation is performed. Analyses of continuous endpoints use the observed values at each visit, so the analysis of covariance at week 24 is restricted to the subjects with both a baseline and a week 24 value. The time-to-event analysis uses the censoring rule stated in the primary endpoint section above.

Cox, D. R. 1972. ‘Regression Models and Life-Tables’. *Journal of the Royal Statistical Society: Series B (Methodological)* 34 (2): 187–220.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 1998. *ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9*. U.S. Food; Drug Administration. https://www.fda.gov/media/71336/download.

Kaplan, E. L., and Paul Meier. 1958. ‘Nonparametric Estimation from Incomplete Observations’. *Journal of the American Statistical Association* 53 (282): 457–81. https://doi.org/10.2307/2281868.