NORDVALE
THERAPEUTICS

PROTOCOL NVT-AD-3001

Clinical Study Report

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

STUDY PHASE
Phase 2

INDICATION
Mild to moderate Alzheimer's disease

SPONSOR
Nordvale Therapeutics

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Draft
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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
0.1	2026-06-15	First draft for internal review.
1.0	2026-07-28	Statistical results added after 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

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Clinical Study Lead
Clinical Development

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Medical Monitor
Clinical Safety and Pharmacovigilance

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Report information

The report that follows summarises the conduct, efficacy and safety results of study NVT-AD-3001. It follows the structure of ICH E3 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use 1995), abbreviated to the sections that carry analysis results.

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1 Synopsis

Protocol number	NVT-AD-3001
Study title	A 24-week, randomised, double-blind, placebo-controlled study of xanomeline transdermal therapeutic system in patients with mild to moderate Alzheimer's disease
Sponsor	Nordvale Therapeutics
Investigational product	Xanomeline transdermal therapeutic system (TTS)
Study phase	Phase 2
Indication	Mild to moderate Alzheimer's disease
Study design	Randomised, double-blind, placebo-controlled, three parallel groups
Treatment groups	Placebo, xanomeline low dose (50 cm2), xanomeline high dose (75 cm2)
Planned duration of treatment	24 weeks
Primary endpoint	Time to first dermatologic treatment-emergent adverse event
Secondary endpoint	Change from baseline in systolic blood pressure at week 24
Analysis populations	Randomised (intention-to-treat), safety and per-protocol populations
Statistical methods	Kaplan-Meier estimation and Cox proportional hazards for the primary endpoint; analysis of covariance for the secondary endpoint

1.1 Subject disposition and key results

A total of 254 subjects were randomised and 254 received at least one dose of study drug. Of these, 110 subjects (43.3%) completed the 24-week treatment period.

At least one treatment-emergent adverse event was reported for 217 subjects (85.4%), and 98 subjects (38.6%) reported at least one dermatologic treatment-emergent adverse event. Dermatologic events occurred earlier and more frequently in both xanomeline groups than in the placebo group, which is consistent with the transdermal route of administration.

No new safety signal was identified beyond the application-site and dermatologic events expected for this formulation.

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2 Ethics and study administration

2.1 Independent ethics committee

The protocol, the informed consent form and all subject-facing material were reviewed and approved by the independent ethics committee or institutional review board responsible for each participating site before any subject was enrolled. Substantial amendments were submitted for approval before implementation.

2.2 Ethical conduct of the study

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH guideline for Good Clinical Practice, and applicable local regulatory requirements.

2.3 Subject information and consent

Written informed consent was obtained from every subject, or from a legally acceptable representative where the subject was unable to provide consent, before any study-specific procedure was performed.

2.4 Study administrative structure

Study conduct was overseen by the sponsor's clinical development team, with data management, statistical programming and medical writing performed by the sponsor. Statistical analyses reported here were produced with the open-source R packages listed in Section B.

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3 Study objectives and design

3.1 Objectives

The primary objective was to characterise the dermatologic tolerability of the xanomeline transdermal therapeutic system over 24 weeks of treatment in patients with mild to moderate Alzheimer's disease.

The secondary objective was to describe the effect of xanomeline on vital signs, expressed as change from baseline in systolic blood pressure at week 24.

3.2 Overall design

The study was a randomised, double-blind, placebo-controlled, parallel-group study conducted at multiple sites. Eligible subjects were randomised in equal proportions to placebo, xanomeline low dose or xanomeline high dose, and were treated for 24 weeks.

Assessments were scheduled at baseline and at weeks 2, 4, 6, 8, 12, 16, 20, 24 and 26. Adverse events were collected throughout the treatment period and for 30 days after the last dose.

3.3 Selection of the study population

Subjects were eligible if they had a diagnosis of probable Alzheimer's disease of mild to moderate severity, were able to comply with the visit schedule, and had a caregiver able to support study participation. Subjects with clinically significant dermatologic conditions at the application site were excluded.

3.4 Disposition of subjects

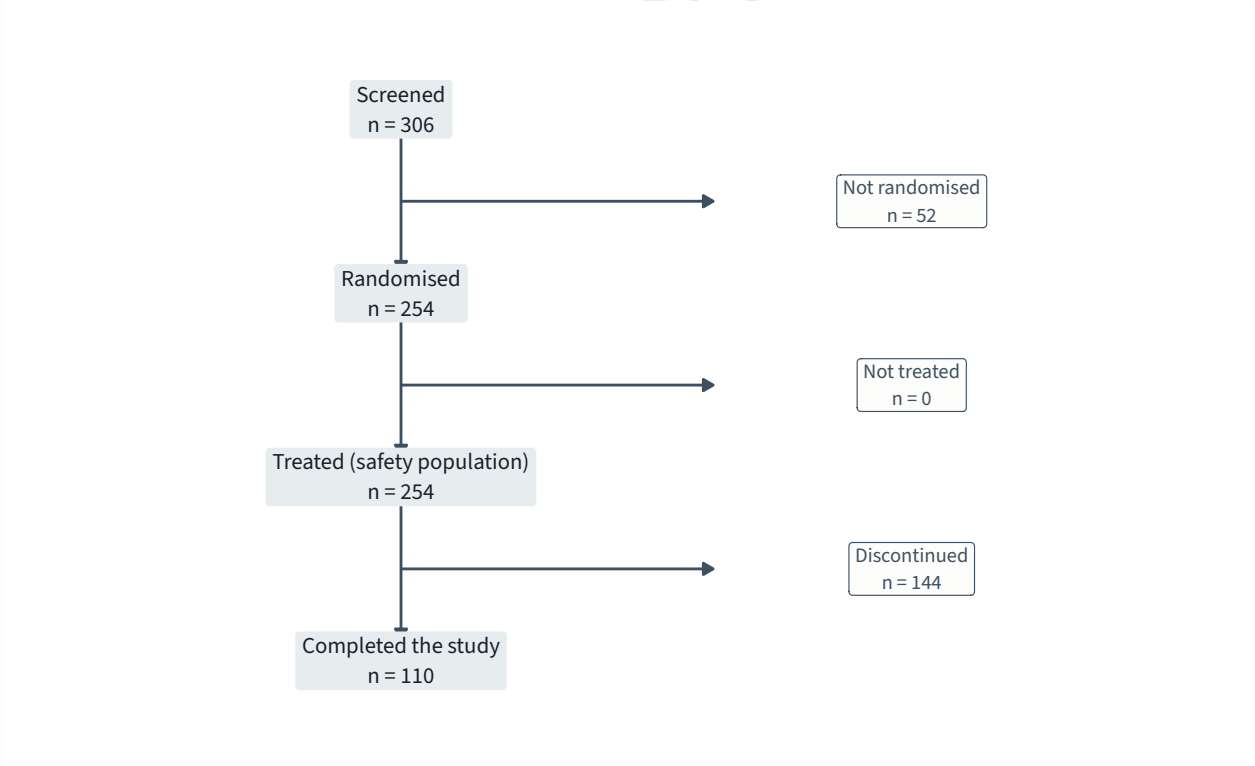

Figure 14.1.1: Disposition of subjects from screening to study completion [Schulz et al. (2010)].

4 Statistical methods

Analyses follow the statistical principles of ICH E9 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use 1998) and were pre-specified in the Statistical Analysis Plan (SAP), finalised before database lock. This chapter narrates the analyses the SAP specified; sections below cite the corresponding SAP section.

4.1 Analysis populations

The randomised population comprises all randomised subjects, analysed according to the treatment to which they were randomised; this is also the intention-to-treat (ITT) population, since every randomised subject received at least one dose of study drug (per SAP Section 3.1). The safety population comprises all randomised subjects who received at least one dose of study drug, analysed according to the treatment actually received (per SAP Section 3.2). The two populations therefore contain the same subjects but do not group them identically: planned and actual treatment differ for the subjects noted in the study patients chapter, so the randomised and safety group sizes differ even though the total does not. The per-protocol (PP) population comprises safety-population subjects who completed the study without discontinuing early; the only protocol deviation information available for this demonstration is discontinuation for protocol violation, and those subjects are already excluded as non-completers, so the PP population is approximated as safety-population completers (per SAP Section 3.3).

Population, disposition, baseline and efficacy outputs use the randomised population by planned treatment; safety outputs use the safety population by actual treatment. The primary endpoint is analysed on the ITT population, with a supportive analysis repeated on the PP population.

4.2 Primary endpoint

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 (per SAP Section 4.1). It is derived from adverse event data, so it is a safety endpoint analysed with efficacy methods; it is presented as the primary endpoint of this demonstration because the pilot data carry no efficacy measure. Subjects without such an event are censored at the last date known to be alive.

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) (per SAP Section 4.2). As a supportive analysis, the same Cox model is repeated on the per-protocol population to assess the sensitivity of the primary result to early discontinuation, and the treatment effect is further examined within sex and age-group subgroups (per SAP Section 4.3).

4.3 Secondary endpoint

Change from baseline in systolic blood pressure at week 24 is analysed with an analysis of covariance model including treatment group as a factor and the baseline value as a covariate (per SAP Section 5.2). 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 secondary endpoint is descriptive, so the two comparisons against placebo are not adjusted for multiplicity. Blood pressure is measured in three postures, each with its own baseline; the analysis uses the supine measurement, so each subject contributes one observation.

4.4 Safety analyses

Adverse events are summarised by system organ class and preferred term, by maximum severity, by relationship to study drug, and separately for serious events (per SAP Section 6). Adverse event, concomitant medication and medical history tables report the terms reached by at least 5% of the subjects in any one treatment group; applying the threshold to the pooled population would hide a term concentrated in a single group. Laboratory, vital signs and electrocardiogram data are summarised as shifts from the baseline reference-range category to the worst post-baseline category, and laboratory data are additionally screened against the aminotransferase and bilirubin criteria for potential drug-induced liver injury.

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4.5 Handling of missing data

No imputation is performed (per SAP Section 7). 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, and time-to-event analyses use the censoring rule stated above.

4.6 Software

All analyses were produced in R with the pharmaverse packages. Analysis data are the CDISC pilot ADaM datasets distributed in `pharmaverseadam`, with the time-to-event dataset derived using `admiral` and the reason for discontinuation taken from the SDTM disposition domain in `pharmaversesdtm`. Summary tables are computed with `gtsummary`, which retains the underlying Analysis Results Datasets, and rendered with `gt`. Each table, listing and figure sits in a Quarto cross-reference div, so every reference to it resolves; titles, populations, source notes and ICH E3 output numbers come from a single index, `R/tlf-index.R`, and the `tlf-numbers.lua` filter numbers each output with the ICH E3 number recorded there. Package versions are listed in Section B.

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5 Study patients

5.1 Analysis populations

Table 14.1.1: Analysis populations. Randomised population.

Population	Placebo N = 86 [1]	Xanomeline Low Dose N = 84 [1]	Xanomeline High Dose N = 84 [1]	Overall N = 254 [1]
Randomised	86 (100%)	84 (100%)	84 (100%)	254 (100%)
Intention-to-treat population	86 (100%)	84 (100%)	84 (100%)	254 (100%)
Safety population	86 (100%)	84 (100%)	84 (100%)	254 (100%)
Per-protocol population	58 (67%)	25 (30%)	27 (32%)	110 (43%)

[1] n (%)

Percentages use the number of randomised subjects in each treatment group as denominator. Every randomised subject received at least one dose of study drug, so the randomised, intention-to-treat and safety populations contain the same subjects; they are counted here under planned treatment, whereas safety outputs count them under actual treatment.

Every randomised subject received at least one dose of study drug, so the randomised, intention-to-treat and safety populations contain the same subjects. They are not interchangeable in the tables that follow: population tables and efficacy analyses count subjects under the treatment to which they were randomised, whereas safety analyses count them under the treatment actually received, and 12 subjects randomised to the high dose received the low dose instead.

5.2 Disposition of subjects

Table 14.1.2: Subject disposition. Randomised population.

Disposition	Placebo N = 86 [1]	Xanomeline Low Dose N = 84 [1]	Xanomeline High Dose N = 84 [1]	Overall N = 254 [1]
Randomised	86 (100%)	84 (100%)	84 (100%)	254 (100%)
Treated (safety population)	86 (100%)	84 (100%)	84 (100%)	254 (100%)
Completed the study	58 (67%)	25 (30%)	27 (32%)	110 (43%)
Discontinued the study	28 (33%)	59 (70%)	57 (68%)	144 (57%)
Reason for discontinuation				
Adverse event	8 (29%)	44 (75%)	40 (70%)	92 (64%)
Withdrawal by subject	9 (32%)	10 (17%)	8 (14%)	27 (19%)
Study terminated by sponsor	2 (7.1%)	2 (3.4%)	3 (5.3%)	7 (4.9%)
Protocol violation	2 (7.1%)	1 (1.7%)	3 (5.3%)	6 (4.2%)
Lack of efficacy	3 (11%)	0 (0%)	1 (1.8%)	4 (2.8%)
Death	2 (7.1%)	1 (1.7%)	0 (0%)	3 (2.1%)

[1] n (%)

Percentages use the number of randomised subjects in each treatment group as denominator, except for the reasons for discontinuation, which use the number of subjects who discontinued in that group and therefore sum to 100%. Reasons come from the disposition domain; the pilot ADSL does not carry them.

Disposition	Placebo N = 86[1]	Xanomeline Low Dose N = 84[1]	Xanomeline High Dose N = 84[1]	Overall N = 254[1]
Physician decision	1 (3.6%)	0 (0%)	2 (3.5%)	3 (2.1%)
Lost to follow-up	1 (3.6%)	1 (1.7%)	0 (0%)	2 (1.4%)
Died	2 (2.3%)	1 (1.2%)	0 (0%)	3 (1.2%)

[1] n (%)

Percentages use the number of randomised subjects in each treatment group as denominator, except for the reasons for discontinuation, which use the number of subjects who discontinued in that group and therefore sum to 100%. Reasons come from the disposition domain; the pilot ADSL does not carry them.

144 subjects discontinued the study before the end of the treatment period, and 3 deaths were reported. The most frequent reason for discontinuation was adverse event, recorded for 92 of the 144 subjects who discontinued, and discontinuation was more frequent in the xanomeline groups than in the placebo group.

5.3 Protocol deviations

The pilot study underlying this demonstration ships no protocol deviation dataset, so deviations can be reported only where they ended a subject's participation. 6 subjects discontinued for a protocol violation; they are listed in Listing 16.2.2.1. Deviations that did not lead to discontinuation cannot be counted here, so no statement is made about their number or their effect on the primary endpoint.

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6 Demographic and baseline characteristics

Table 14.1.3: Demographic and baseline characteristics. Randomised population.

Characteristic	Placebo N = 86 [1]	Xanomeline Low Dose N = 84 [1]	Xanomeline High Dose N = 84 [1]	Overall N = 254 [1]
Age (years)	75.2 (8.6); 76.0 [52.0, 89.0]	75.7 (8.3); 77.5 [51.0, 88.0]	74.4 (7.9); 76.0 [56.0, 88.0]	75.1 (8.2); 77.0 [51.0, 89.0]
Age group (years)				
18-64	14 (16%)	8 (9.5%)	11 (13%)	33 (13%)
>64	72 (84%)	76 (90%)	73 (87%)	221 (87%)
Sex				
Female	53 (62%)	50 (60%)	40 (48%)	143 (56%)
Male	33 (38%)	34 (40%)	44 (52%)	111 (44%)
Race				
AMERICAN INDIAN OR ALASKA NATIVE	0 (0%)	0 (0%)	1 (1.2%)	1 (0.4%)
BLACK OR AFRICAN AMERICAN	8 (9.3%)	6 (7.1%)	9 (11%)	23 (9.1%)
WHITE	78 (91%)	78 (93%)	74 (88%)	230 (91%)
Ethnicity				
HISPANIC OR LATINO	3 (3.5%)	6 (7.1%)	3 (3.6%)	12 (4.7%)
NOT HISPANIC OR LATINO	83 (97%)	78 (93%)	81 (96%)	242 (95%)
Treatment duration (days)	149.5 (60.4); 182.0 [7.0, 210.0]	97.3 (68.3); 81.0 [2.0, 212.0]	98.2 (70.8); 76.0 [1.0, 200.0]	115.2 (70.7); 132.0 [1.0, 212.0]

[1] Mean (SD); Median [Min, Max]; n (%)

Continuous variables are summarised as mean (standard deviation); median [minimum, maximum].

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The treatment groups were comparable at baseline. The mean age was 75.1 years and 143 subjects (56.3%) were female, with no clinically relevant imbalance between groups in age, sex, race or ethnicity.

6.1 Medical history

Table 14.1.4: Medical history by body system and preferred term. Conditions reported by at least 5% of subjects in any treatment group, randomised population.

Body system / preferred term	Placebo N = 86 [1]	Xanomeline Low Dose N = 84 [1]	Xanomeline High Dose N = 84 [1]
Any medical history finding	80 (93%)	80 (95%)	83 (99%)
Cardiac disorders	17 (20%)	23 (27%)	17 (20%)
Myocardial infarction	7 (8.1%)	10 (12%)	5 (6.0%)
Ear and labyrinth disorders	16 (19%)	12 (14%)	22 (26%)

[1] n (%)

Subjects reporting more than one condition within a body system or preferred term are counted once. Percentages use the number of randomised subjects in each treatment group as denominator. The primary diagnosis of Alzheimer's disease is recorded for every subject and is excluded, since it is the indication rather than a medical history finding. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

Body system / preferred term	Placebo N = 86 [1]	Xanomeline Low Dose N = 84 [1]	Xanomeline High Dose N = 84 [1]
Deafness	4 (4.7%)	4 (4.8%)	6 (7.1%)
Deafness bilateral	0 (0%)	1 (1.2%)	5 (6.0%)
Hypoacusis	5 (5.8%)	3 (3.6%)	4 (4.8%)
Tinnitus	1 (1.2%)	5 (6.0%)	4 (4.8%)
Endocrine disorders	7 (8.1%)	10 (12%)	8 (9.5%)
Hypothyroidism	6 (7.0%)	8 (9.5%)	7 (8.3%)
Eye disorders	26 (30%)	26 (31%)	28 (33%)
Cataract	6 (7.0%)	8 (9.5%)	4 (4.8%)
Glaucoma	7 (8.1%)	6 (7.1%)	6 (7.1%)
Hypermetropia	2 (2.3%)	3 (3.6%)	6 (7.1%)
Macular degeneration	5 (5.8%)	1 (1.2%)	2 (2.4%)
Gastrointestinal disorders	29 (34%)	29 (35%)	28 (33%)
Constipation	6 (7.0%)	6 (7.1%)	8 (9.5%)
Dyspepsia	10 (12%)	2 (2.4%)	5 (6.0%)
General disorders and administration site conditions	10 (12%)	12 (14%)	7 (8.3%)
Chest pain	0 (0%)	0 (0%)	5 (6.0%)
Oedema peripheral	7 (8.1%)	7 (8.3%)	1 (1.2%)
Infections and infestations	16 (19%)	15 (18%)	14 (17%)
Pneumonia	7 (8.1%)	1 (1.2%)	2 (2.4%)
Sinusitis	5 (5.8%)	4 (4.8%)	3 (3.6%)
Investigations	7 (8.1%)	12 (14%)	20 (24%)
Cardiac murmur	3 (3.5%)	3 (3.6%)	7 (8.3%)
Metabolism and nutrition disorders	12 (14%)	8 (9.5%)	16 (19%)
Diabetes mellitus	1 (1.2%)	1 (1.2%)	7 (8.3%)
Hypercholesterolaemia	7 (8.1%)	4 (4.8%)	5 (6.0%)
Musculoskeletal and connective tissue disorders	37 (43%)	41 (49%)	40 (48%)
Arthritis	14 (16%)	19 (23%)	14 (17%)
Osteoarthritis	7 (8.1%)	7 (8.3%)	6 (7.1%)
Polyarthritis	3 (3.5%)	5 (6.0%)	5 (6.0%)
Nervous system disorders	20 (23%)	17 (20%)	24 (29%)
Dizziness	3 (3.5%)	5 (6.0%)	8 (9.5%)
Headache	9 (10%)	9 (11%)	11 (13%)
Reproductive system and breast disorders	7 (8.1%)	10 (12%)	8 (9.5%)

[1] n (%)

Subjects reporting more than one condition within a body system or preferred term are counted once. Percentages use the number of randomised subjects in each treatment group as denominator. The primary diagnosis of Alzheimer's disease is recorded for every subject and is excluded, since it is the indication rather than a medical history finding. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

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Body system / preferred term	Placebo N = 86 [1]	Xanomeline Low Dose N = 84 [1]	Xanomeline High Dose N = 84 [1]
Benign prostatic hyperplasia	5 (5.8%)	6 (7.1%)	7 (8.3%)
Surgical and medical procedures	45 (52%)	59 (70%)	55 (65%)
Appendicectomy	8 (9.3%)	4 (4.8%)	11 (13%)
Cataract operation	10 (12%)	6 (7.1%)	4 (4.8%)
Haemorrhoid operation	0 (0%)	2 (2.4%)	5 (6.0%)
Hernia repair	5 (5.8%)	3 (3.6%)	7 (8.3%)
Hysterectomy	9 (10%)	13 (15%)	12 (14%)
Tonsillectomy	7 (8.1%)	8 (9.5%)	6 (7.1%)
Transurethral prostatectomy	1 (1.2%)	5 (6.0%)	3 (3.6%)
Vascular disorders	22 (26%)	20 (24%)	27 (32%)
Hypertension	21 (24%)	16 (19%)	25 (30%)

[1] n (%)

Subjects reporting more than one condition within a body system or preferred term are counted once. Percentages use the number of randomised subjects in each treatment group as denominator. The primary diagnosis of Alzheimer's disease is recorded for every subject and is excluded, since it is the indication rather than a medical history finding. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

Reported medical history was consistent with an elderly population and was distributed similarly across the treatment groups.

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7 Primary and secondary endpoints

7.1 Primary endpoint: time to first dermatologic event

Table 14.2.1: Time to first dermatologic treatment-emergent adverse event. Intention-to-treat population.

Treatment group	Subjects	Subjects with an event	Median time to event (days)	Hazard ratio (95% CI)	p-value
Placebo	86	20 (23.3%)	Not reached	Reference	
Xanomeline Low Dose	84	39 (46.4%)	80 (55, NA)	2.98 (1.73, 5.13)	<0.001
Xanomeline High Dose	84	39 (46.4%)	89 (50, NA)	3.34 (1.94, 5.75)	<0.001

Medians and confidence intervals are Kaplan-Meier estimates. Hazard ratios come from a Cox proportional hazards model with planned treatment as the only covariate and placebo as the reference group. A median is reported as not reached where fewer than half the subjects in the group had an event.

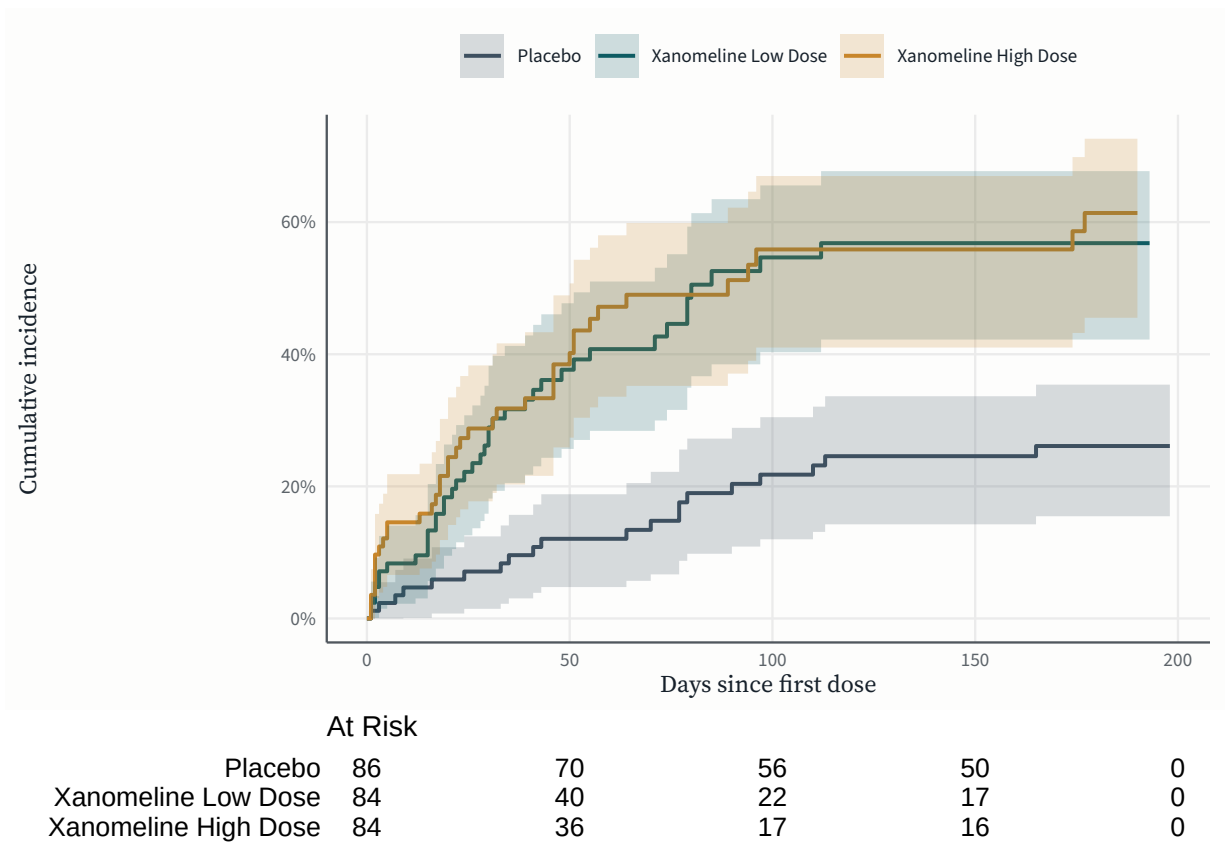

Figure 14.2.1: Cumulative incidence of the first dermatologic treatment-emergent adverse event, intention-to-treat population.

Both xanomeline groups reached a higher cumulative incidence of dermatologic events than placebo, and the separation appeared within the first weeks of treatment. The hazard ratios in Table 14.2.1 quantify that difference; the confidence intervals exclude one for both dose groups.

2 subjects have a last date known to be alive that precedes their first dose in the source data, and are censored at day 1 rather than excluded, which is the behaviour of `admiral::derive_param_tte()`. They enter the risk set for the first day only, so their influence on the estimates is negligible without being nil.

7.1.1 Supportive analysis: per-protocol population

Table 14.2.1.1: Time to first dermatologic treatment-emergent adverse event (supportive analysis). Per-protocol population.

Treatment group	Subjects	Subjects with an event	Median time to event (days)	Hazard ratio (95% CI)	p-value
Placebo	58	11 (19.0%)	Not reached	Reference	
Xanomeline Low Dose	25	10 (40.0%)	Not reached	2.65 (1.12, 6.23)	0.026
Xanomeline High Dose	27	15 (55.6%)	174 (46, NA)	3.87 (1.77, 8.43)	<0.001

Medians and confidence intervals are Kaplan-Meier estimates. Hazard ratios come from a Cox proportional hazards model with planned treatment as the only covariate and placebo as the reference group. The per-protocol population is restricted to safety-population subjects who completed the study.

The per-protocol result in Table 14.2.1.1 is consistent in direction and magnitude with the intention-to-treat result in Table 14.2.1, supporting the primary conclusion.

7.1.2 Subgroup analysis

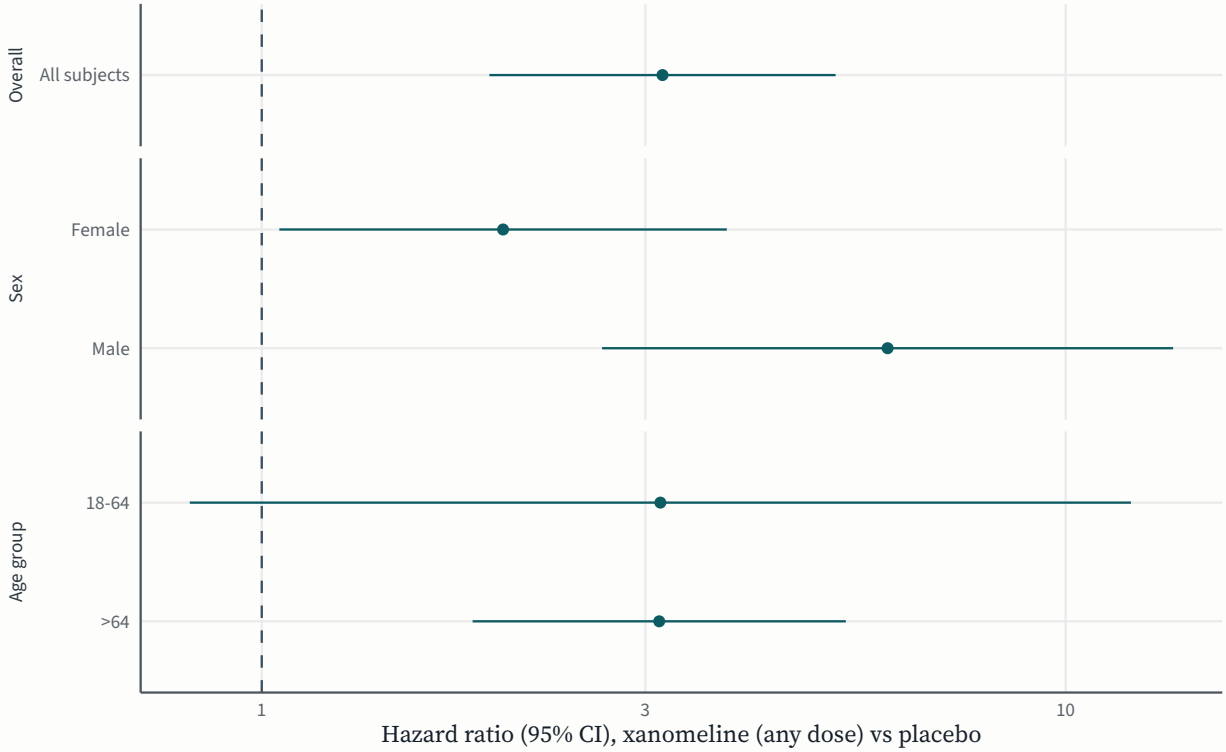

Figure 14.2.2: Hazard ratio for the primary endpoint by age group and sex, intention-to-treat population.

The treatment effect on the primary endpoint was consistent across sex and age-group subgroups, with no confidence interval crossing the line of no effect.

7.2 Secondary endpoint: change in systolic blood pressure

Table 14.2.2: Change from baseline in supine systolic blood pressure at week 24. Safety population.

Treatment group	n	LS mean change (SE)	95% CI	Difference versus placebo (95% CI)	p-value
Placebo	59	−2.02 (1.88)	(−5.75, 1.71)	Reference	
Xanomeline Low Dose	25	−0.99 (2.90)	(−6.74, 4.76)	1.03 (-5.83, 7.90)	0.77
Xanomeline High Dose	28	−5.47 (2.73)	(−10.89, −0.05)	−3.45 (-10.02, 3.13)	0.30

Least-squares means from an analysis of covariance model with actual treatment group as a factor and the baseline value as a covariate. n is the number of subjects with both a baseline and a week 24 supine value; no values are imputed. Vital signs are measured in three postures, each with its own baseline; the model uses the supine measurement, so each subject contributes one observation.

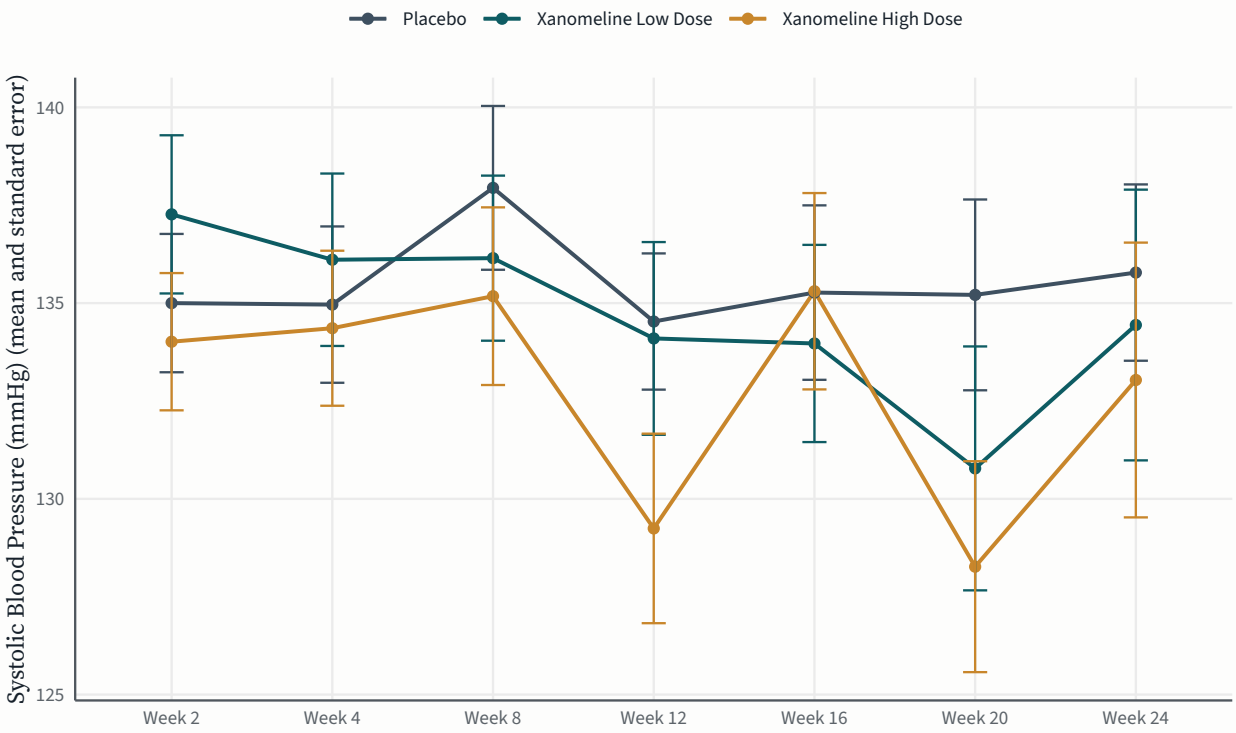

Figure 14.2.3: Mean supine systolic blood pressure by visit and treatment group, safety population.

Mean systolic blood pressure remained stable across the treatment period in all three groups. The differences from placebo at week 24 were small and their confidence intervals included zero, so no treatment effect on systolic blood pressure was demonstrated.

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8 Safety evaluation

Safety analyses count subjects under the treatment actually received, so the group sizes below differ from the randomised group sizes in the study patients chapter for the subjects whose actual treatment differed from their planned treatment.

8.1 Extent of exposure

Table 14.3.5: Extent of exposure. Safety population.

Exposure	Placebo N = 86 [1]	Xanomeline Low Dose N = 96 [1]	Xanomeline High Dose N = 72 [1]
Exposure (days)	147.8 (62.1); 182.0 [0.0, 210.0]	85.9 (70.7); 62.5 [0.0, 212.0]	112.2 (65.5); 96.5 [15.0, 200.0]
Exposure category			
0	1 (1.2%)	1 (1.0%)	0 (0%)
1 to 28	7 (8.1%)	28 (29%)	5 (6.9%)
29 to 84	11 (13%)	27 (28%)	29 (40%)
85 to 168	8 (9.3%)	15 (16%)	10 (14%)
>168	59 (69%)	25 (26%)	28 (39%)

[1] Mean (SD); Median [Min, Max]; n (%)

Exposure is the total treatment duration in days, derived from the exposure analysis dataset. Category percentages use the number of safety-population subjects in each treatment group as denominator, so they sum to 100%.

8.2 Prior and concomitant medications

Table 14.3.6: Prior and concomitant medications by drug class and preferred term. Medications taken by at least 5% of subjects in any treatment group, safety population.

Drug class / preferred term	Placebo N = 86 [1]	Xanomeline Low Dose N = 96 [1]	Xanomeline High Dose N = 72 [1]
Any prior or concomitant medication	77 (90%)	86 (90%)	66 (92%)
Alimentary tract and metabolism	12 (14%)	12 (13%)	8 (11%)
Calcium	7 (8.1%)	6 (6.3%)	3 (4.2%)
Nizatidine	1 (1.2%)	1 (1.0%)	4 (5.6%)
Cardiovascular system	12 (14%)	13 (14%)	6 (8.3%)
Amlodipine	8 (9.3%)	1 (1.0%)	2 (2.8%)
Genito urinary system and sex hormones	6 (7.0%)	10 (10%)	5 (6.9%)
Estrogens conjugated	6 (7.0%)	10 (10%)	5 (6.9%)
Nervous system	23 (27%)	14 (15%)	8 (11%)
Acetylsalicylic acid	21 (24%)	11 (11%)	6 (8.3%)
Systemic hormonal preparations, excl.	2 (2.3%)	13 (14%)	8 (11%)
Hydrocortisone	2 (2.3%)	13 (14%)	8 (11%)

[1] n (%)

Subjects taking more than one medication within a drug class or preferred term are counted once. Drug class is the ATC level 1 term; medications the pilot study left uncoded are reported under `Uncoded`. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

DRAFT

Drug class / preferred term	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]
Uncoded	74 (86%)	82 (85%)	65 (90%)
Uncoded	74 (86%)	82 (85%)	65 (90%)

[1] n (%)

Subjects taking more than one medication within a drug class or preferred term are counted once. Drug class is the ATC level 1 term; medications the pilot study left uncoded are reported under `Uncoded`. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

Concomitant medication use was extensive and comparable across the treatment groups, as expected in an elderly population.

8.3 Overview of adverse events

Table 14.3.1.1: Overview of treatment-emergent adverse events. Safety population.

Subjects with at least one event	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Overall N = 254[1]
Any treatment-emergent adverse event (TEAE)	65 (76%)	84 (88%)	68 (94%)	217 (85%)
Any serious TEAE	0 (0%)	2 (2.1%)	1 (1.4%)	3 (1.2%)
Any severe TEAE	5 (5.8%)	16 (17%)	8 (11%)	29 (11%)
Any drug-related TEAE	43 (50%)	77 (80%)	64 (89%)	184 (72%)
Any TEAE leading to withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any dermatologic TEAE	20 (23%)	39 (41%)	39 (54%)	98 (39%)
Any TEAE with fatal outcome	2 (2.3%)	1 (1.0%)	0 (0%)	3 (1.2%)

DRAFT

[1] n (%)

Subjects are counted once in each row. A treatment-emergent adverse event started on or after the first dose of study drug.

8.4 Adverse events by system organ class and preferred term

Table 14.3.1.2: Treatment-emergent adverse events by system organ class and preferred term. Events reported by at least 5% of subjects in any treatment group, safety population.

System organ class / preferred term	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]
Any treatment-emergent adverse event	65 (76%)	84 (88%)	68 (94%)
Cardiac disorders	12 (14%)	14 (15%)	14 (19%)
Myocardial infarction	4 (4.7%)	2 (2.1%)	4 (5.6%)
Sinus bradycardia	2 (2.3%)	7 (7.3%)	8 (11%)
Gastrointestinal disorders	17 (20%)	15 (16%)	19 (26%)
Diarrhoea	9 (10%)	5 (5.2%)	3 (4.2%)

[1] n (%)

Subjects reporting more than one event within a system organ class or preferred term are counted once. Percentages use the number of safety-population subjects in each treatment group as denominator. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

System organ class / preferred term	Placebo N = 86 [1]	Xanomeline Low Dose N = 96 [1]	Xanomeline High Dose N = 72 [1]
Nausea	3 (3.5%)	3 (3.1%)	6 (8.3%)
Salivary hypersecretion	0 (0%)	0 (0%)	4 (5.6%)
Vomiting	3 (3.5%)	4 (4.2%)	6 (8.3%)
General disorders and administration site conditions	21 (24%)	51 (53%)	36 (50%)
Application site dermatitis	5 (5.8%)	9 (9.4%)	7 (9.7%)
Application site erythema	3 (3.5%)	13 (14%)	14 (19%)
Application site irritation	3 (3.5%)	9 (9.4%)	9 (13%)
Application site pruritus	6 (7.0%)	23 (24%)	21 (29%)
Application site vesicles	1 (1.2%)	5 (5.2%)	5 (6.9%)
Fatigue	1 (1.2%)	5 (5.2%)	5 (6.9%)
Infections and infestations	16 (19%)	9 (9.4%)	13 (18%)
Nasopharyngitis	2 (2.3%)	4 (4.2%)	6 (8.3%)
Upper respiratory tract infection	6 (7.0%)	1 (1.0%)	3 (4.2%)
Nervous system disorders	8 (9.3%)	22 (23%)	23 (32%)
Dizziness	2 (2.3%)	9 (9.4%)	10 (14%)
Headache	3 (3.5%)	3 (3.1%)	5 (6.9%)
Syncope	0 (0%)	5 (5.2%)	2 (2.8%)
Respiratory, thoracic and mediastinal disorders	8 (9.3%)	9 (9.4%)	10 (14%)
Cough	1 (1.2%)	5 (5.2%)	5 (6.9%)
Skin and subcutaneous tissue disorders	20 (23%)	39 (41%)	39 (54%)
Blister	0 (0%)	5 (5.2%)	1 (1.4%)
Erythema	8 (9.3%)	14 (15%)	14 (19%)
Hyperhidrosis	2 (2.3%)	4 (4.2%)	8 (11%)
Pruritus	8 (9.3%)	21 (22%)	25 (35%)
Rash	5 (5.8%)	13 (14%)	8 (11%)
Skin irritation	3 (3.5%)	6 (6.3%)	5 (6.9%)

[1] n (%)

Subjects reporting more than one event within a system organ class or preferred term are counted once. Percentages use the number of safety-population subjects in each treatment group as denominator. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

Application-site and other dermatologic events dominated the adverse event profile in both xanomeline groups. The pattern is consistent with the transdermal delivery system and with the primary endpoint result in Table 14.2.1.

8.5 Adverse events by maximum severity

Table 14.3.1.3: Treatment-emergent adverse events by maximum severity. Events reported by at least 5% of subjects in any treatment group, safety population.

DRAFT

System organ class / preferred term	Mild			Moderate			Severe		
	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]
Any treatment-emergent adverse event	58 (67%)	58 (60%)	60 (83%)	25 (29%)	54 (56%)	45 (63%)	5 (5.8%)	16 (17%)	8 (11%)
Cardiac disorders	9 (10%)	12 (13%)	8 (11%)	3 (3.5%)	5 (5.2%)	5 (6.9%)	2 (2.3%)	0 (0%)	1 (1.4%)
Myocardial infarction	1 (1.2%)	2 (2.1%)	3 (4.2%)	1 (1.2%)	0 (0%)	1 (1.4%)	2 (2.3%)	0 (0%)	0 (0%)
Sinus bradycardia	1 (1.2%)	6 (6.3%)	4 (5.6%)	1 (1.2%)	1 (1.0%)	4 (5.6%)			
Gastrointestinal disorders	15 (17%)	10 (10%)	15 (21%)	2 (2.3%)	5 (5.2%)	3 (4.2%)	0 (0%)	0 (0%)	2 (2.8%)
Diarrhoea	9 (10%)	4 (4.2%)	2 (2.8%)	0 (0%)	1 (1.0%)	1 (1.4%)			
Nausea	2 (2.3%)	2 (2.1%)	5 (6.9%)	1 (1.2%)	1 (1.0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)
Salivary hypersecretion	0 (0%)	0 (0%)	4 (5.6%)						
Vomiting	2 (2.3%)	2 (2.1%)	5 (6.9%)	1 (1.2%)	2 (2.1%)	1 (1.4%)			
General disorders and administration site conditions	18 (21%)	27 (28%)	25 (35%)	5 (5.8%)	23 (24%)	19 (26%)	0 (0%)	7 (7.3%)	0 (0%)
Application site dermatitis	5 (5.8%)	4 (4.2%)	2 (2.8%)	0 (0%)	4 (4.2%)	5 (6.9%)	0 (0%)	1 (1.0%)	0 (0%)
Application site erythema	3 (3.5%)	4 (4.2%)	9 (13%)	0 (0%)	7 (7.3%)	5 (6.9%)	0 (0%)	2 (2.1%)	0 (0%)
Application site irritation	1 (1.2%)	3 (3.1%)	3 (4.2%)	2 (2.3%)	3 (3.1%)	6 (8.3%)	0 (0%)	3 (3.1%)	0 (0%)

[1] n (%)

Subjects reporting more than one event within a preferred term are counted once, under the highest severity reported for that term. Percentages use the number of safety-population subjects in each treatment group as denominator. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

DRAFT

System organ class / preferred term	Mild			Moderate			Severe		
	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]
Application site pruritus	5 (5.8%)	13 (14%)	10 (14%)	1 (1.2%)	9 (9.4%)	11 (15%)	0 (0%)	1 (1.0%)	0 (0%)
Application site vesicles	1 (1.2%)	3 (3.1%)	2 (2.8%)	0 (0%)	2 (2.1%)	3 (4.2%)			
Fatigue	1 (1.2%)	3 (3.1%)	5 (6.9%)	0 (0%)	2 (2.1%)	0 (0%)			
Infections and infestations	12 (14%)	6 (6.3%)	10 (14%)	5 (5.8%)	2 (2.1%)	3 (4.2%)	0 (0%)	1 (1.0%)	0 (0%)
Nasopharyngitis	1 (1.2%)	3 (3.1%)	5 (6.9%)	1 (1.2%)	0 (0%)	1 (1.4%)	0 (0%)	1 (1.0%)	0 (0%)
Upper respiratory tract infection	4 (4.7%)	1 (1.0%)	2 (2.8%)	2 (2.3%)	0 (0%)	1 (1.4%)			
Nervous system disorders	6 (7.0%)	14 (15%)	17 (24%)	2 (2.3%)	9 (9.4%)	7 (9.7%)	0 (0%)	3 (3.1%)	4 (5.6%)
Dizziness	2 (2.3%)	6 (6.3%)	6 (8.3%)	0 (0%)	3 (3.1%)	3 (4.2%)	0 (0%)	0 (0%)	1 (1.4%)
Headache	3 (3.5%)	2 (2.1%)	4 (5.6%)	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)	1 (1.0%)	0 (0%)
Syncope	0 (0%)	1 (1.0%)	0 (0%)	0 (0%)	2 (2.1%)	1 (1.4%)	0 (0%)	2 (2.1%)	1 (1.4%)
Respiratory, thoracic and mediastinal disorders	7 (8.1%)	7 (7.3%)	8 (11%)	1 (1.2%)	3 (3.1%)	2 (2.8%)			
Cough	1 (1.2%)	3 (3.1%)	3 (4.2%)	0 (0%)	2 (2.1%)	2 (2.8%)			
Skin and subcutaneous tissue disorders	15 (17%)	16 (17%)	32 (44%)	8 (9.3%)	24 (25%)	15 (21%)	0 (0%)	4 (4.2%)	1 (1.4%)
Blister	0 (0%)	1 (1.0%)	1 (1.4%)	0 (0%)	3 (3.1%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)
Erythema	4 (4.7%)	6 (6.3%)	10 (14%)	4 (4.7%)	8 (8.3%)	4 (5.6%)			
Hyperhidrosis	2 (2.3%)	1 (1.0%)	8 (11%)	0 (0%)	3 (3.1%)	0 (0%)			
Pruritus	7 (8.1%)	9 (9.4%)	16 (22%)	1 (1.2%)	11 (11%)	9 (13%)	0 (0%)	1 (1.0%)	0 (0%)

[1] n (%)

Subjects reporting more than one event within a preferred term are counted once, under the highest severity reported for that term. Percentages use the number of safety-population subjects in each treatment group as denominator. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

DRAFT

System organ class / preferred term	Mild			Moderate			Severe		
	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]
Rash	2 (2.3%)	9 (9.4%)	5 (6.9%)	3 (3.5%)	3 (3.1%)	2 (2.8%)	0 (0%)	1 (1.0%)	1 (1.4%)
Skin irritation	2 (2.3%)	2 (2.1%)	3 (4.2%)	1 (1.2%)	3 (3.1%)	2 (2.8%)	0 (0%)	1 (1.0%)	0 (0%)

[1] n (%)

Subjects reporting more than one event within a preferred term are counted once, under the highest severity reported for that term. Percentages use the number of safety-population subjects in each treatment group as denominator. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

8.6 Adverse events by relationship to study drug

Table 14.3.1.4: Treatment-emergent adverse events by relationship to study drug. Events reported by at least 5% of subjects in any treatment group, safety population.

System organ class / preferred term	Related			Not related		
	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]
Any treatment-emergent adverse event	43 (50%)	77 (80%)	64 (89%)	50 (58%)	48 (50%)	46 (64%)
Cardiac disorders	6 (7.0%)	8 (8.3%)	3 (4.2%)	6 (7.0%)	8 (8.3%)	11 (15%)
Myocardial infarction	2 (2.3%)	1 (1.0%)	1 (1.4%)	2 (2.3%)	1 (1.0%)	3 (4.2%)
Sinus bradycardia	2 (2.3%)	2 (2.1%)	0 (0%)	0 (0%)	5 (5.2%)	8 (11%)
Gastrointestinal disorders	4 (4.7%)	8 (8.3%)	9 (13%)	13 (15%)	7 (7.3%)	10 (14%)
Diarrhoea	3 (3.5%)	3 (3.1%)	1 (1.4%)	6 (7.0%)	2 (2.1%)	2 (2.8%)
Nausea	0 (0%)	3 (3.1%)	3 (4.2%)	3 (3.5%)	0 (0%)	3 (4.2%)
Salivary hypersecretion	0 (0%)	0 (0%)	3 (4.2%)	0 (0%)	0 (0%)	1 (1.4%)
Vomiting	0 (0%)	3 (3.1%)	2 (2.8%)	3 (3.5%)	1 (1.0%)	4 (5.6%)
General disorders and administration site conditions	18 (21%)	45 (47%)	33 (46%)	4 (4.7%)	11 (11%)	8 (11%)
Application site dermatitis	5 (5.8%)	9 (9.4%)	7 (9.7%)			
Application site erythema	3 (3.5%)	13 (14%)	14 (19%)			

[1] n (%)

Subjects reporting more than one event within a preferred term are counted once, as related if any event for that term was investigator-assessed as related. Percentages use the number of safety-population subjects in each treatment group as denominator. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

DRAFT

System organ class / preferred term	Related			Not related		
	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]
Application site irritation	3 (3.5%)	9 (9.4%)	9 (13%)			
Application site pruritus	6 (7.0%)	23 (24%)	21 (29%)			
Application site vesicles	1 (1.2%)	5 (5.2%)	5 (6.9%)			
Fatigue	1 (1.2%)	2 (2.1%)	4 (5.6%)	0 (0%)	3 (3.1%)	1 (1.4%)
Nervous system disorders	4 (4.7%)	14 (15%)	13 (18%)	5 (5.8%)	9 (9.4%)	14 (19%)
Dizziness	2 (2.3%)	7 (7.3%)	5 (6.9%)	0 (0%)	2 (2.1%)	5 (6.9%)
Headache	1 (1.2%)	1 (1.0%)	1 (1.4%)	2 (2.3%)	2 (2.1%)	4 (5.6%)
Syncope	0 (0%)	5 (5.2%)	2 (2.8%)			
Skin and subcutaneous tissue disorders	16 (19%)	37 (39%)	38 (53%)	7 (8.1%)	4 (4.2%)	4 (5.6%)
Blister	0 (0%)	5 (5.2%)	1 (1.4%)			
Erythema	8 (9.3%)	13 (14%)	14 (19%)	0 (0%)	1 (1.0%)	0 (0%)
Hyperhidrosis	1 (1.2%)	4 (4.2%)	8 (11%)	1 (1.2%)	0 (0%)	0 (0%)
Pruritus	7 (8.1%)	20 (21%)	25 (35%)	1 (1.2%)	1 (1.0%)	0 (0%)
Rash	3 (3.5%)	11 (11%)	6 (8.3%)	2 (2.3%)	2 (2.1%)	2 (2.8%)
Skin irritation	2 (2.3%)	6 (6.3%)	5 (6.9%)	1 (1.2%)	0 (0%)	0 (0%)
Infections and infestations				16 (19%)	9 (9.4%)	13 (18%)
Nasopharyngitis				2 (2.3%)	4 (4.2%)	6 (8.3%)
Upper respiratory tract infection				6 (7.0%)	1 (1.0%)	3 (4.2%)
Respiratory, thoracic and mediastinal disorders				6 (7.0%)	9 (9.4%)	10 (14%)
Cough				1 (1.2%)	5 (5.2%)	5 (6.9%)

[1] n (%)

Subjects reporting more than one event within a preferred term are counted once, as related if any event for that term was investigator-assessed as related. Percentages use the number of safety-population subjects in each treatment group as denominator. The overall row and the rows for each class count every subject with a qualifying record, including subjects whose only terms fall below the reporting threshold and are therefore not shown.

8.7 Serious adverse events and deaths

Table 14.3.1.5: Serious treatment-emergent adverse events. Safety population.

DRAFT

Preferred term	Placebo N = 86 [1]	Xanomeline Low Dose N = 96 [1]	Xanomeline High Dose N = 72 [1]
Any serious treatment-emergent adverse event	0 (0%)	2 (2.1%)	1 (1.4%)
Partial seizures with secondary generalisation	0 (0%)	0 (0%)	1 (1.4%)
Syncope	0 (0%)	2 (2.1%)	0 (0%)

[1] n (%)

Seriousness was assessed by the investigator according to the protocol definition.

Subject-level detail for every serious event is listed in Listing 16.2.7.1.

8.7.1 Narratives

ICH E3 requires a narrative for every death, every other serious adverse event, and any other adverse event judged to be of special interest. Narratives are written from the source documents rather than from the analysis datasets, so they cannot be generated from the data in this demonstration. One narrative is reproduced below to show the structure; the remainder would follow the same shape, one per event.

> **Note**
>
> **Subject 01-701-XXXX, placebo, serious adverse event.** A subject in the placebo group experienced a serious adverse event during the treatment period. The event began on the study day recorded in Listing 16.2.7.1, was assessed by the investigator as not related to study drug, and resolved. Study drug was not withdrawn and the subject continued in the study.
>
> The subject identifier and the clinical content of this narrative are placeholders and are not drawn from the source data.

8.8 Laboratory evaluations

Table 14.3.4.1: Shift from baseline to worst post-baseline category. Alanine aminotransferase, safety population.

	Low			Normal			High		
Characteristic	Placebo N = 0 [1]	Xanomeline Low Dose N = 1 [1]	Xanomeline High Dose N = 0 [1]	Placebo N = 80 [1]	Xanomeline Low Dose N = 89 [1]	Xanomeline High Dose N = 68 [1]	Placebo N = 4 [1]	Xanomeline Low Dose N = 3 [1]	Xanomeline High Dose N = 4 [1]
Worst post-baseline category									
Low	0 (NA%)	0 (0%)	0 (NA%)	1 (1.3%)	5 (5.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (NA%)	1 (100%)	0 (NA%)	73 (91%)	76 (85%)	61 (90%)	1 (25%)	0 (0%)	0 (0%)
High	0 (NA%)	0 (0%)	0 (NA%)	6 (7.5%)	8 (9.0%)	7 (10%)	3 (75%)	3 (100%)	4 (100%)

[1] n (%)

Categories are relative to the reference range of the reporting laboratory. The worst post-baseline category is high if any post-baseline value was high, otherwise low if any value was low. Percentages use the number of subjects in each baseline category and treatment group as denominator, so they sum to 100% within each baseline category.

Table 14.3.4.2: Shift from baseline to worst post-baseline category. Aspartate aminotransferase, safety population.

Characteristic	Normal			High		
	Placebo N = 78[1]	Xanomeline Low Dose N = 85[1]	Xanomeline High Dose N = 69[1]	Placebo N = 6[1]	Xanomeline Low Dose N = 8[1]	Xanomeline High Dose N = 3[1]
Worst post-baseline category						
Low	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Normal	70 (90%)	76 (89%)	63 (91%)	2 (33%)	3 (38%)	1 (33%)
High	8 (10%)	9 (11%)	5 (7.2%)	4 (67%)	5 (63%)	2 (67%)

[1] n (%)

Categories are relative to the reference range of the reporting laboratory. The worst post-baseline category is high if any post-baseline value was high, otherwise low if any value was low. Percentages use the number of subjects in each baseline category and treatment group as denominator, so they sum to 100% within each baseline category.

Table 14.3.4.3: Shift from baseline to worst post-baseline category. Bilirubin, safety population.

Characteristic	Normal			High		
	Placebo N = 82[1]	Xanomeline Low Dose N = 89[1]	Xanomeline High Dose N = 69[1]	Placebo N = 2[1]	Xanomeline Low Dose N = 3[1]	Xanomeline High Dose N = 3[1]
Worst post-baseline category						
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	78 (95%)	88 (99%)	67 (97%)	0 (0%)	2 (67%)	0 (0%)
High	4 (4.9%)	1 (1.1%)	2 (2.9%)	2 (100%)	1 (33%)	3 (100%)

[1] n (%)

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Categories are relative to the reference range of the reporting laboratory. The worst post-baseline category is high if any post-baseline value was high, otherwise low if any value was low. Percentages use the number of subjects in each baseline category and treatment group as denominator, so they sum to 100% within each baseline category.

Table 14.3.4.4: Shift from baseline to worst post-baseline category. Creatinine, safety population.

Characteristic	Low			Normal			High		
	Placebo N = 2[1]	Xanomeline Low Dose N = 0[1]	Xanomeline High Dose N = 1[1]	Placebo N = 81[1]	Xanomeline Low Dose N = 88[1]	Xanomeline High Dose N = 66[1]	Placebo N = 1[1]	Xanomeline Low Dose N = 5[1]	Xanomeline High Dose N = 5[1]
Worst post-baseline category									
Low	1 (50%)	0 (NA%)	1 (100%)	1 (1.2%)	1 (1.1%)	2 (3.0%)	0 (0%)	0 (0%)	0 (0%)
Normal	1 (50%)	0 (NA%)	0 (0%)	72 (89%)	82 (93%)	56 (85%)	0 (0%)	0 (0%)	0 (0%)
High	0 (0%)	0 (NA%)	0 (0%)	8 (9.9%)	5 (5.7%)	8 (12%)	1 (100%)	5 (100%)	5 (100%)

[1] n (%)

Categories are relative to the reference range of the reporting laboratory. The worst post-baseline category is high if any post-baseline value was high, otherwise low if any value was low. Percentages use the number of subjects in each baseline category and treatment group as denominator, so they sum to 100% within each baseline category.

Shifts to a high category were infrequent for each analyte in this panel and distributed similarly across treatment groups.

Table 14.3.4.5: Potential drug-induced liver injury. Safety population.

Subjects meeting the criterion	Placebo N = 86[1]	Xanomeline Low Dose N = 96[1]	Xanomeline High Dose N = 72[1]	Overall N = 254[1]
Alanine aminotransferase at least 3 x ULN	2 (2.3%)	0 (0%)	1 (1.4%)	3 (1.2%)
Aspartate aminotransferase at least 3 x ULN	2 (2.3%)	1 (1.0%)	1 (1.4%)	4 (1.6%)
Total bilirubin at least 2 x ULN	1 (1.2%)	0 (0%)	1 (1.4%)	2 (0.8%)
Aminotransferase at least 3 x ULN with bilirubin at least 2 x ULN	1 (1.2%)	0 (0%)	0 (0%)	1 (0.4%)

[1] n (%)

Counts are of subjects with at least one post-baseline value meeting each criterion, relative to the upper limit of the reference range of the reporting laboratory. The combined criterion requires an aminotransferase elevation and a bilirubin elevation in the same subject, not necessarily on the same day, and is a screen for potential drug-induced liver injury rather than a diagnosis.

Subjects meeting the combined aminotransferase and bilirubin criterion: 1, in the following treatment groups: placebo. 5 subjects met at least one criterion in total, too few for the difference between treatment groups to be interpretable, so the laboratory data show no signal of xanomeline-related liver injury. Subject-level values for every subject meeting any criterion are listed in Listing 16.2.8.1.

8.9 Vital signs

Table 14.3.7: Shift from baseline to worst post-baseline category. Systolic blood pressure measured supine, safety population.

	Normal			High		
Characteristic	Placebo N = 26[1]	Xanomeline Low Dose N = 22[1]	Xanomeline High Dose N = 22[1]	Placebo N = 57[1]	Xanomeline Low Dose N = 53[1]	Xanomeline High Dose N = 50[1]
Worst post-baseline category						
Low	1 (3.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	10 (38%)	8 (36%)	13 (59%)	2 (3.5%)	4 (7.5%)	6 (12%)
High	15 (58%)	14 (64%)	9 (41%)	55 (96%)	49 (92%)	44 (88%)

[1] n (%)

Categories are relative to the reference range of the reporting site. The worst post-baseline category is high (hypertensive) if any post-baseline value was high, otherwise low (hypotensive) if any value was low. Percentages use the number of subjects in each baseline category and treatment group as denominator, so they sum to 100% within each baseline category. Vital signs are measured in three postures, each with its own baseline; this table uses the supine measurement, so a subject is counted once.

Shifts to a high systolic blood pressure category occurred at a similar rate across treatment groups, with no excess of new hypotensive or hypertensive categories in either xanomeline group relative to placebo.

8.10 Electrocardiogram

Table 14.3.8: Shift from baseline to worst post-baseline category. QTcF interval, safety population.

Characteristic	Normal			High		
	Placebo N = 0[1]	Xanomeline Low Dose N = 0[1]	Xanomeline High Dose N = 1[1]	Placebo N = 84[1]	Xanomeline Low Dose N = 94[1]	Xanomeline High Dose N = 71[1]
Worst post-baseline category						
Low	0 (NA%)	0 (NA%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (NA%)	0 (NA%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
High	0 (NA%)	0 (NA%)	1 (100%)	84 (100%)	94 (100%)	71 (100%)

[1] n (%)

Categories are relative to the reference range of the reporting site. The worst post-baseline category is high if any post-baseline value was high, otherwise low if any value was low. Percentages use the number of subjects in each baseline category and treatment group as denominator, so they sum to 100% within each baseline category.

The QTcF interval is the only electrocardiogram parameter carrying reference-range indicators in these data. Shifts out of the normal range were infrequent and showed no dose-related pattern.

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9 Discussion and overall conclusions

Over 24 weeks of double-blind treatment in 254 subjects with mild to moderate Alzheimer's disease, the dermatologic tolerability of the xanomeline transdermal therapeutic system was the dominant safety finding. 98 subjects reported at least one dermatologic treatment-emergent adverse event, and the events began earlier in both xanomeline groups than in the placebo group.

Serious treatment-emergent adverse events were reported for 3 subjects, without a pattern suggesting a treatment-related excess. Laboratory, vital sign and electrocardiogram findings did not identify a new safety concern, no subject in a xanomeline group met the combined biochemical criterion for potential drug-induced liver injury, and systolic blood pressure was unchanged relative to placebo at week 24.

The results support the conclusion that dermatologic tolerability is the limiting factor for this formulation at the doses studied. Any further development of the transdermal route should address application-site tolerability, for example by modifying the adhesive system or the rotation schedule of application sites.

> **Note**
>
> This report is a demonstration of Quarto for regulated reporting. The conclusions describe the public CDISC pilot data used to build it and are not a statement about any real medicinal product.

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10 Reference list

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A Listings

A.1 Individual subject data listings

Listing 16.2.1.1: Subjects who discontinued the study. Randomised population.

Subject	Treatment	Age (years)	Sex	Treatment duration (days)	Reason for discontinuation
01-701-1023	Placebo	64	Male	28	Adverse event
01-701-1047	Placebo	85	Female	26	Adverse event
01-701-1345	Placebo	63	Female	162	Study terminated by sponsor
01-701-1387	Placebo	87	Female	14	Protocol violation
01-703-1096	Placebo	81	Female	51	Lost to follow-up
01-703-1175	Placebo	75	Male	7	Protocol violation
01-704-1010	Placebo	80	Male	138	Withdrawal by subject
01-704-1233	Placebo	87	Female	15	Withdrawal by subject
01-704-1260	Placebo	71	Female	67	Withdrawal by subject
01-704-1435	Placebo	74	Male	54	Withdrawal by subject
01-704-1445	Placebo	75	Male	175	Death
01-705-1018	Placebo	69	Female	NA	Withdrawal by subject
01-705-1059	Placebo	66	Female	123	Adverse event
01-705-1186	Placebo	84	Female	19	Physician decision
01-708-1158	Placebo	81	Female	42	Adverse event
01-708-1378	Placebo	67	Male	148	Study terminated by sponsor
01-709-1259	Placebo	82	Male	139	Lack of efficacy
01-709-1306	Placebo	60	Female	134	Adverse event
01-710-1083	Placebo	89	Female	11	Death
01-710-1264	Placebo	78	Male	121	Adverse event
01-710-1271	Placebo	86	Female	56	Adverse event
01-710-1314	Placebo	78	Female	30	Withdrawal by subject
01-710-1315	Placebo	83	Female	130	Adverse event
01-715-1155	Placebo	59	Female	44	Withdrawal by subject
01-716-1308	Placebo	76	Female	41	Withdrawal by subject
01-717-1201	Placebo	85	Female	65	Lack of efficacy
01-717-1344	Placebo	64	Female	63	Lack of efficacy
01-718-1172	Placebo	74	Male	70	Withdrawal by subject
01-701-1033	Xanomeline Low Dose	74	Male	14	Study terminated by sponsor
01-701-1111	Xanomeline Low Dose	81	Female	10	Adverse event
01-701-1115	Xanomeline Low Dose	84	Male	55	Adverse event
01-701-1188	Xanomeline Low Dose	71	Male	38	Adverse event
01-701-1211	Xanomeline Low Dose	76	Female	59	Death
01-701-1294	Xanomeline Low Dose	67	Male	83	Adverse event
01-701-1341	Xanomeline Low Dose	51	Male	22	Adverse event
01-701-1429	Xanomeline Low Dose	84	Female	43	Withdrawal by subject

One row per subject. Reasons come from the disposition domain.

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Subject	Treatment	Age (years)	Sex	Treatment duration (days)	Reason for discontinuation
01-702-1082	Xanomeline Low Dose	84	Female	80	Withdrawal by subject
01-703-1086	Xanomeline Low Dose	71	Male	94	Adverse event
01-703-1119	Xanomeline Low Dose	81	Female	114	Adverse event
01-703-1182	Xanomeline Low Dose	84	Male	56	Adverse event
01-703-1197	Xanomeline Low Dose	76	Female	14	Withdrawal by subject
01-703-1279	Xanomeline Low Dose	72	Female	22	Withdrawal by subject
01-704-1009	Xanomeline Low Dose	83	Male	30	Withdrawal by subject
01-704-1025	Xanomeline Low Dose	81	Female	28	Adverse event
01-704-1114	Xanomeline Low Dose	77	Male	166	Withdrawal by subject
01-704-1120	Xanomeline Low Dose	71	Female	62	Adverse event
01-704-1323	Xanomeline Low Dose	68	Female	29	Adverse event
01-704-1325	Xanomeline Low Dose	81	Male	73	Protocol violation
01-705-1031	Xanomeline Low Dose	56	Female	22	Lost to follow-up
01-705-1199	Xanomeline Low Dose	87	Male	13	Adverse event
01-705-1393	Xanomeline Low Dose	84	Female	148	Adverse event
01-706-1384	Xanomeline Low Dose	74	Female	10	Adverse event
01-707-1037	Xanomeline Low Dose	72	Female	5	Withdrawal by subject
01-708-1019	Xanomeline Low Dose	68	Male	13	Adverse event
01-708-1032	Xanomeline Low Dose	62	Male	21	Adverse event
01-708-1272	Xanomeline Low Dose	82	Male	45	Withdrawal by subject
01-708-1297	Xanomeline Low Dose	61	Male	99	Adverse event
01-708-1353	Xanomeline Low Dose	87	Female	56	Adverse event
01-708-1428	Xanomeline Low Dose	84	Female	36	Adverse event
01-709-1007	Xanomeline Low Dose	54	Female	29	Adverse event
01-709-1081	Xanomeline Low Dose	86	Female	100	Adverse event
01-709-1102	Xanomeline Low Dose	71	Female	72	Adverse event
01-709-1217	Xanomeline Low Dose	77	Male	100	Adverse event
01-709-1285	Xanomeline Low Dose	87	Male	61	Study terminated by sponsor
01-710-1002	Xanomeline Low Dose	88	Male	5	Adverse event
01-710-1045	Xanomeline Low Dose	83	Female	72	Adverse event
01-710-1053	Xanomeline Low Dose	84	Female	47	Adverse event
01-710-1154	Xanomeline Low Dose	84	Male	30	Adverse event
01-710-1166	Xanomeline Low Dose	81	Female	110	Adverse event
01-710-1270	Xanomeline Low Dose	83	Female	18	Adverse event
01-710-1300	Xanomeline Low Dose	78	Female	63	Adverse event
01-710-1358	Xanomeline Low Dose	82	Male	146	Withdrawal by subject
01-710-1385	Xanomeline Low Dose	77	Male	113	Adverse event
01-711-1143	Xanomeline Low Dose	76	Female	58	Adverse event
01-713-1448	Xanomeline Low Dose	71	Female	118	Adverse event
01-714-1068	Xanomeline Low Dose	79	Female	62	Adverse event
01-715-1107	Xanomeline Low Dose	65	Male	71	Adverse event

One row per subject. Reasons come from the disposition domain.

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Subject	Treatment	Age (years)	Sex	Treatment duration (days)	Reason for discontinuation
01-715-1405	Xanomeline Low Dose	69	Male	2	Adverse event
01-716-1063	Xanomeline Low Dose	80	Male	109	Adverse event
01-716-1094	Xanomeline Low Dose	82	Male	37	Adverse event
01-716-1151	Xanomeline Low Dose	83	Female	100	Adverse event
01-716-1298	Xanomeline Low Dose	76	Female	82	Adverse event
01-716-1311	Xanomeline Low Dose	78	Male	131	Withdrawal by subject
01-718-1066	Xanomeline Low Dose	79	Female	10	Adverse event
01-718-1079	Xanomeline Low Dose	67	Female	43	Adverse event
01-718-1170	Xanomeline Low Dose	80	Female	27	Adverse event
01-718-1250	Xanomeline Low Dose	82	Female	133	Adverse event
01-701-1146	Xanomeline High Dose	75	Female	38	Adverse event
01-701-1180	Xanomeline High Dose	56	Male	35	Adverse event
01-701-1181	Xanomeline High Dose	79	Female	5	Adverse event
01-701-1275	Xanomeline High Dose	61	Male	114	Withdrawal by subject
01-701-1302	Xanomeline High Dose	61	Male	69	Adverse event
01-701-1360	Xanomeline High Dose	67	Male	6	Physician decision
01-701-1444	Xanomeline High Dose	63	Male	39	Adverse event
01-703-1076	Xanomeline High Dose	69	Male	61	Adverse event
01-703-1258	Xanomeline High Dose	78	Female	176	Adverse event
01-703-1295	Xanomeline High Dose	88	Female	150	Withdrawal by subject
01-703-1335	Xanomeline High Dose	67	Female	52	Protocol violation
01-703-1403	Xanomeline High Dose	67	Male	2	Adverse event
01-704-1008	Xanomeline High Dose	76	Female	40	Adverse event
01-704-1017	Xanomeline High Dose	77	Male	44	Adverse event
01-704-1065	Xanomeline High Dose	75	Male	60	Adverse event
01-704-1074	Xanomeline High Dose	80	Female	58	Adverse event
01-704-1093	Xanomeline High Dose	79	Male	95	Adverse event
01-704-1241	Xanomeline High Dose	86	Male	46	Adverse event
01-704-1266	Xanomeline High Dose	82	Male	55	Adverse event
01-704-1332	Xanomeline High Dose	80	Male	68	Adverse event
01-705-1281	Xanomeline High Dose	73	Female	92	Adverse event
01-705-1303	Xanomeline High Dose	72	Male	15	Adverse event
01-705-1310	Xanomeline High Dose	74	Female	83	Adverse event
01-705-1377	Xanomeline High Dose	63	Female	22	Withdrawal by subject
01-705-1382	Xanomeline High Dose	82	Male	NA	Protocol violation
01-706-1049	Xanomeline High Dose	60	Female	36	Adverse event
01-708-1178	Xanomeline High Dose	77	Female	99	Physician decision
01-708-1213	Xanomeline High Dose	76	Female	14	Adverse event
01-708-1216	Xanomeline High Dose	78	Male	37	Adverse event
01-708-1236	Xanomeline High Dose	86	Female	1	Withdrawal by subject
01-708-1347	Xanomeline High Dose	61	Female	60	Adverse event

One row per subject. Reasons come from the disposition domain.

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Subject	Treatment	Age (years)	Sex	Treatment duration (days)	Reason for discontinuation
01-708-1372	Xanomeline High Dose	84	Male	8	Protocol violation
01-709-1168	Xanomeline High Dose	72	Female	56	Adverse event
01-709-1238	Xanomeline High Dose	69	Male	84	Adverse event
01-709-1329	Xanomeline High Dose	70	Male	11	Withdrawal by subject
01-709-1424	Xanomeline High Dose	77	Male	5	Adverse event
01-710-1021	Xanomeline High Dose	79	Male	33	Adverse event
01-710-1070	Xanomeline High Dose	85	Female	137	Adverse event
01-710-1137	Xanomeline High Dose	79	Female	34	Adverse event
01-710-1142	Xanomeline High Dose	76	Female	19	Adverse event
01-710-1278	Xanomeline High Dose	81	Male	65	Adverse event
01-711-1012	Xanomeline High Dose	67	Female	27	Adverse event
01-711-1433	Xanomeline High Dose	84	Female	10	Adverse event
01-713-1141	Xanomeline High Dose	79	Male	32	Adverse event
01-714-1425	Xanomeline High Dose	81	Male	5	Study terminated by sponsor
01-715-1319	Xanomeline High Dose	65	Male	17	Withdrawal by subject
01-715-1321	Xanomeline High Dose	75	Female	70	Adverse event
01-716-1030	Xanomeline High Dose	83	Female	6	Withdrawal by subject
01-716-1071	Xanomeline High Dose	78	Female	55	Adverse event
01-716-1189	Xanomeline High Dose	81	Male	142	Adverse event
01-716-1229	Xanomeline High Dose	73	Female	40	Adverse event
01-716-1373	Xanomeline High Dose	74	Male	76	Adverse event
01-717-1357	Xanomeline High Dose	77	Male	167	Study terminated by sponsor
01-718-1101	Xanomeline High Dose	82	Male	165	Study terminated by sponsor
01-718-1328	Xanomeline High Dose	86	Male	77	Withdrawal by subject
01-718-1371	Xanomeline High Dose	69	Female	98	Adverse event
01-718-1427	Xanomeline High Dose	74	Female	57	Lack of efficacy

One row per subject. Reasons come from the disposition domain.

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Listing 16.2.2.1: Subjects who discontinued for a protocol violation. Randomised population.

Subject	Treatment	Age (years)	Sex	Treatment duration (days)	End of study status
01-701-1387	Placebo	87	Female	14	Discontinued
01-703-1175	Placebo	75	Male	7	Discontinued
01-704-1325	Xanomeline Low Dose	81	Male	73	Discontinued
01-703-1335	Xanomeline High Dose	67	Female	52	Discontinued
01-705-1382	Xanomeline High Dose	82	Male	NA	Discontinued
01-708-1372	Xanomeline High Dose	84	Male	8	Discontinued

The pilot study ships no protocol deviation dataset, so this listing covers only violations severe enough to end study participation. Deviations that did not lead to discontinuation cannot be listed.

Listing 16.2.4.1: Demographic data. Randomised population.

Subject	Treatment	Age (years)	Age group	Sex	Race	Completed
01-701-1015	Placebo	63	18-64	Female	White	Yes

One row per subject, in treatment group and subject identifier order.

Subject	Treatment	Age (years)	Age group	Sex	Race	Completed
01-701-1023	Placebo	64	18-64	Male	White	No
01-701-1047	Placebo	85	>64	Female	White	No
01-701-1118	Placebo	52	18-64	Male	White	Yes
01-701-1130	Placebo	84	>64	Male	White	Yes
01-701-1153	Placebo	79	>64	Female	White	Yes
01-701-1203	Placebo	81	>64	Female	Black or african american	Yes
01-701-1234	Placebo	69	>64	Male	White	Yes
01-701-1345	Placebo	63	18-64	Female	White	No
01-701-1363	Placebo	81	>64	Female	Black or african american	Yes
01-701-1387	Placebo	87	>64	Female	White	No
01-701-1392	Placebo	78	>64	Male	White	Yes
01-701-1415	Placebo	85	>64	Male	White	Yes
01-701-1440	Placebo	70	>64	Male	White	Yes
01-703-1042	Placebo	64	18-64	Male	White	Yes
01-703-1096	Placebo	81	>64	Female	White	No
01-703-1100	Placebo	84	>64	Female	White	Yes
01-703-1175	Placebo	75	>64	Male	White	No
01-703-1210	Placebo	72	>64	Female	White	Yes
01-703-1299	Placebo	81	>64	Female	White	Yes
01-704-1010	Placebo	80	>64	Male	White	No
01-704-1127	Placebo	84	>64	Female	White	Yes
01-704-1164	Placebo	67	>64	Female	White	Yes
01-704-1233	Placebo	87	>64	Female	White	No
01-704-1260	Placebo	71	>64	Female	White	No
01-704-1351	Placebo	70	>64	Male	White	Yes
01-704-1388	Placebo	81	>64	Male	White	Yes
01-704-1435	Placebo	74	>64	Male	White	No
01-704-1445	Placebo	75	>64	Male	White	No
01-705-1018	Placebo	69	>64	Female	White	No
01-705-1059	Placebo	66	>64	Female	White	No
01-705-1186	Placebo	84	>64	Female	White	No
01-705-1282	Placebo	70	>64	Female	Black or african american	Yes
01-705-1349	Placebo	86	>64	Female	White	Yes
01-706-1041	Placebo	64	18-64	Female	Black or african american	Yes
01-707-1206	Placebo	65	>64	Male	White	Yes
01-708-1087	Placebo	74	>64	Female	White	Yes
01-708-1158	Placebo	81	>64	Female	White	No
01-708-1171	Placebo	77	>64	Female	White	Yes
01-708-1253	Placebo	61	18-64	Male	White	Yes
01-708-1286	Placebo	80	>64	Female	Black or african american	Yes
01-708-1296	Placebo	57	18-64	Male	Black or african american	Yes

One row per subject, in treatment group and subject identifier order.

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Subject	Treatment	Age (years)	Age group	Sex	Race	Completed
01-708-1316	Placebo	74	>64	Female	White	Yes
01-708-1342	Placebo	59	18-64	Female	White	Yes
01-708-1378	Placebo	67	>64	Male	Black or african american	No
01-709-1001	Placebo	76	>64	Female	White	Yes
01-709-1088	Placebo	69	>64	Male	White	Yes
01-709-1259	Placebo	82	>64	Male	White	No
01-709-1301	Placebo	62	18-64	Female	White	Yes
01-709-1306	Placebo	60	18-64	Female	White	No
01-709-1312	Placebo	68	>64	Female	White	Yes
01-709-1339	Placebo	81	>64	Male	White	Yes
01-710-1027	Placebo	83	>64	Male	White	Yes
01-710-1060	Placebo	82	>64	Male	White	Yes
01-710-1077	Placebo	76	>64	Female	White	Yes
01-710-1078	Placebo	81	>64	Female	White	Yes
01-710-1083	Placebo	89	>64	Female	White	No
01-710-1183	Placebo	80	>64	Female	White	Yes
01-710-1264	Placebo	78	>64	Male	White	No
01-710-1271	Placebo	86	>64	Female	White	No
01-710-1314	Placebo	78	>64	Female	White	No
01-710-1315	Placebo	83	>64	Female	White	No
01-710-1368	Placebo	88	>64	Female	White	Yes
01-711-1036	Placebo	70	>64	Male	Black or african american	Yes
01-713-1179	Placebo	64	18-64	Female	White	Yes
01-713-1256	Placebo	71	>64	Male	White	Yes
01-713-1269	Placebo	73	>64	Male	White	Yes
01-714-1035	Placebo	88	>64	Female	White	Yes
01-714-1375	Placebo	78	>64	Female	White	Yes
01-715-1155	Placebo	59	18-64	Female	White	No
01-715-1207	Placebo	78	>64	Female	White	Yes
01-715-1397	Placebo	76	>64	Female	White	Yes
01-716-1024	Placebo	87	>64	Female	White	Yes
01-716-1026	Placebo	73	>64	Female	White	Yes
01-716-1044	Placebo	74	>64	Male	White	Yes
01-716-1108	Placebo	86	>64	Female	White	Yes
01-716-1160	Placebo	83	>64	Female	White	Yes
01-716-1177	Placebo	72	>64	Male	White	Yes
01-716-1308	Placebo	76	>64	Female	White	No
01-716-1441	Placebo	85	>64	Male	White	Yes
01-717-1201	Placebo	85	>64	Female	White	No
01-717-1344	Placebo	64	18-64	Female	White	No
01-718-1139	Placebo	77	>64	Male	White	Yes

One row per subject, in treatment group and subject identifier order.

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Subject	Treatment	Age (years)	Age group	Sex	Race	Completed
01-718-1150	Placebo	73	>64	Female	White	Yes
01-718-1172	Placebo	74	>64	Male	White	No
01-718-1355	Placebo	79	>64	Male	White	Yes
01-701-1033	Xanomeline Low Dose	74	>64	Male	White	No
01-701-1097	Xanomeline Low Dose	68	>64	Male	White	Yes
01-701-1111	Xanomeline Low Dose	81	>64	Female	White	No
01-701-1115	Xanomeline Low Dose	84	>64	Male	White	No
01-701-1188	Xanomeline Low Dose	71	>64	Male	White	No
01-701-1192	Xanomeline Low Dose	80	>64	Female	White	Yes
01-701-1211	Xanomeline Low Dose	76	>64	Female	White	No
01-701-1294	Xanomeline Low Dose	67	>64	Male	White	No
01-701-1317	Xanomeline Low Dose	68	>64	Male	White	Yes
01-701-1324	Xanomeline Low Dose	79	>64	Male	White	Yes
01-701-1341	Xanomeline Low Dose	51	18-64	Male	White	No
01-701-1429	Xanomeline Low Dose	84	>64	Female	White	No
01-701-1442	Xanomeline Low Dose	57	18-64	Female	Black or african american	Yes
01-702-1082	Xanomeline Low Dose	84	>64	Female	White	No
01-703-1086	Xanomeline Low Dose	71	>64	Male	White	No
01-703-1119	Xanomeline Low Dose	81	>64	Female	White	No
01-703-1182	Xanomeline Low Dose	84	>64	Male	White	No
01-703-1197	Xanomeline Low Dose	76	>64	Female	Black or african american	No
01-703-1279	Xanomeline Low Dose	72	>64	Female	White	No
01-703-1379	Xanomeline Low Dose	81	>64	Female	Black or african american	Yes
01-704-1009	Xanomeline Low Dose	83	>64	Male	White	No
01-704-1025	Xanomeline Low Dose	81	>64	Female	White	No
01-704-1114	Xanomeline Low Dose	77	>64	Male	White	No
01-704-1120	Xanomeline Low Dose	71	>64	Female	White	No
01-704-1135	Xanomeline Low Dose	74	>64	Female	White	Yes
01-704-1218	Xanomeline Low Dose	81	>64	Female	White	Yes
01-704-1323	Xanomeline Low Dose	68	>64	Female	White	No
01-704-1325	Xanomeline Low Dose	81	>64	Male	White	No
01-705-1031	Xanomeline Low Dose	56	18-64	Female	White	No
01-705-1199	Xanomeline Low Dose	87	>64	Male	White	No
01-705-1292	Xanomeline Low Dose	60	18-64	Female	Black or african american	Yes
01-705-1393	Xanomeline Low Dose	84	>64	Female	White	No
01-705-1431	Xanomeline Low Dose	68	>64	Female	White	Yes
01-706-1384	Xanomeline Low Dose	74	>64	Female	White	No
01-707-1037	Xanomeline Low Dose	72	>64	Female	White	No
01-708-1019	Xanomeline Low Dose	68	>64	Male	White	No
01-708-1032	Xanomeline Low Dose	62	18-64	Male	White	No
01-708-1084	Xanomeline Low Dose	73	>64	Female	White	Yes

One row per subject, in treatment group and subject identifier order.

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Subject	Treatment	Age (years)	Age group	Sex	Race	Completed
01-708-1272	Xanomeline Low Dose	82	>64	Male	White	No
01-708-1297	Xanomeline Low Dose	61	18-64	Male	White	No
01-708-1348	Xanomeline Low Dose	79	>64	Female	White	Yes
01-708-1353	Xanomeline Low Dose	87	>64	Female	Black or african american	No
01-708-1428	Xanomeline Low Dose	84	>64	Female	White	No
01-709-1007	Xanomeline Low Dose	54	18-64	Female	White	No
01-709-1020	Xanomeline Low Dose	72	>64	Female	White	Yes
01-709-1081	Xanomeline Low Dose	86	>64	Female	White	No
01-709-1102	Xanomeline Low Dose	71	>64	Female	White	No
01-709-1217	Xanomeline Low Dose	77	>64	Male	White	No
01-709-1285	Xanomeline Low Dose	87	>64	Male	White	No
01-709-1326	Xanomeline Low Dose	75	>64	Female	White	Yes
01-710-1002	Xanomeline Low Dose	88	>64	Male	White	No
01-710-1045	Xanomeline Low Dose	83	>64	Female	White	No
01-710-1053	Xanomeline Low Dose	84	>64	Female	White	No
01-710-1154	Xanomeline Low Dose	84	>64	Male	White	No
01-710-1166	Xanomeline Low Dose	81	>64	Female	White	No
01-710-1235	Xanomeline Low Dose	56	18-64	Female	White	Yes
01-710-1270	Xanomeline Low Dose	83	>64	Female	White	No
01-710-1300	Xanomeline Low Dose	78	>64	Female	White	No
01-710-1358	Xanomeline Low Dose	82	>64	Male	White	No
01-710-1385	Xanomeline Low Dose	77	>64	Male	White	No
01-711-1143	Xanomeline Low Dose	76	>64	Female	White	No
01-713-1043	Xanomeline Low Dose	78	>64	Female	White	Yes
01-713-1073	Xanomeline Low Dose	74	>64	Female	Black or african american	Yes
01-713-1448	Xanomeline Low Dose	71	>64	Female	White	No
01-714-1068	Xanomeline Low Dose	79	>64	Female	White	No
01-714-1195	Xanomeline Low Dose	75	>64	Male	White	Yes
01-715-1085	Xanomeline Low Dose	77	>64	Female	White	Yes
01-715-1107	Xanomeline Low Dose	65	>64	Male	White	No
01-715-1405	Xanomeline Low Dose	69	>64	Male	White	No
01-716-1063	Xanomeline Low Dose	80	>64	Male	White	No
01-716-1094	Xanomeline Low Dose	82	>64	Male	White	No
01-716-1103	Xanomeline Low Dose	79	>64	Male	White	Yes
01-716-1151	Xanomeline Low Dose	83	>64	Female	White	No
01-716-1157	Xanomeline Low Dose	85	>64	Male	White	Yes
01-716-1167	Xanomeline Low Dose	68	>64	Male	White	Yes
01-716-1298	Xanomeline Low Dose	76	>64	Female	White	No
01-716-1311	Xanomeline Low Dose	78	>64	Male	White	No
01-717-1004	Xanomeline Low Dose	80	>64	Female	White	Yes
01-717-1446	Xanomeline Low Dose	75	>64	Female	White	Yes

One row per subject, in treatment group and subject identifier order.

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Subject	Treatment	Age (years)	Age group	Sex	Race	Completed
01-718-1066	Xanomeline Low Dose	79	>64	Female	White	No
01-718-1079	Xanomeline Low Dose	67	>64	Female	White	No
01-718-1170	Xanomeline Low Dose	80	>64	Female	White	No
01-718-1250	Xanomeline Low Dose	82	>64	Female	White	No
01-718-1254	Xanomeline Low Dose	78	>64	Male	White	Yes
01-701-1028	Xanomeline High Dose	71	>64	Male	White	Yes
01-701-1034	Xanomeline High Dose	77	>64	Female	White	Yes
01-701-1133	Xanomeline High Dose	81	>64	Female	White	Yes
01-701-1146	Xanomeline High Dose	75	>64	Female	White	No
01-701-1148	Xanomeline High Dose	57	18-64	Male	White	Yes
01-701-1180	Xanomeline High Dose	56	18-64	Male	White	No
01-701-1181	Xanomeline High Dose	79	>64	Female	White	No
01-701-1239	Xanomeline High Dose	56	18-64	Male	White	Yes
01-701-1275	Xanomeline High Dose	61	18-64	Male	American indian or alaska native	No
01-701-1287	Xanomeline High Dose	56	18-64	Female	White	Yes
01-701-1302	Xanomeline High Dose	61	18-64	Male	White	No
01-701-1360	Xanomeline High Dose	67	>64	Male	White	No
01-701-1383	Xanomeline High Dose	72	>64	Female	White	Yes
01-701-1444	Xanomeline High Dose	63	18-64	Male	White	No
01-703-1076	Xanomeline High Dose	69	>64	Male	White	No
01-703-1258	Xanomeline High Dose	78	>64	Female	White	No
01-703-1295	Xanomeline High Dose	88	>64	Female	White	No
01-703-1335	Xanomeline High Dose	67	>64	Female	Black or african american	No
01-703-1403	Xanomeline High Dose	67	>64	Male	White	No
01-703-1439	Xanomeline High Dose	76	>64	Female	White	Yes
01-704-1008	Xanomeline High Dose	76	>64	Female	White	No
01-704-1017	Xanomeline High Dose	77	>64	Male	White	No
01-704-1065	Xanomeline High Dose	75	>64	Male	White	No
01-704-1074	Xanomeline High Dose	80	>64	Female	White	No
01-704-1093	Xanomeline High Dose	79	>64	Male	White	No
01-704-1241	Xanomeline High Dose	86	>64	Male	White	No
01-704-1266	Xanomeline High Dose	82	>64	Male	White	No
01-704-1332	Xanomeline High Dose	80	>64	Male	White	No
01-705-1280	Xanomeline High Dose	56	18-64	Female	White	Yes
01-705-1281	Xanomeline High Dose	73	>64	Female	Black or african american	No
01-705-1303	Xanomeline High Dose	72	>64	Male	White	No
01-705-1310	Xanomeline High Dose	74	>64	Female	White	No
01-705-1377	Xanomeline High Dose	63	18-64	Female	Black or african american	No
01-705-1382	Xanomeline High Dose	82	>64	Male	White	No
01-706-1049	Xanomeline High Dose	60	18-64	Female	White	No
01-708-1178	Xanomeline High Dose	77	>64	Female	Black or african american	No

One row per subject, in treatment group and subject identifier order.

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Subject	Treatment	Age (years)	Age group	Sex	Race	Completed
01-708-1213	Xanomeline High Dose	76	>64	Female	White	No
01-708-1216	Xanomeline High Dose	78	>64	Male	White	No
01-708-1236	Xanomeline High Dose	86	>64	Female	White	No
01-708-1336	Xanomeline High Dose	73	>64	Male	White	Yes
01-708-1347	Xanomeline High Dose	61	18-64	Female	White	No
01-708-1372	Xanomeline High Dose	84	>64	Male	White	No
01-708-1406	Xanomeline High Dose	71	>64	Female	White	Yes
01-709-1029	Xanomeline High Dose	82	>64	Male	White	Yes
01-709-1099	Xanomeline High Dose	79	>64	Female	White	Yes
01-709-1168	Xanomeline High Dose	72	>64	Female	White	No
01-709-1238	Xanomeline High Dose	69	>64	Male	White	No
01-709-1309	Xanomeline High Dose	65	>64	Male	White	Yes
01-709-1329	Xanomeline High Dose	70	>64	Male	White	No
01-709-1424	Xanomeline High Dose	77	>64	Male	White	No
01-710-1006	Xanomeline High Dose	77	>64	Male	White	Yes
01-710-1021	Xanomeline High Dose	79	>64	Male	Black or african american	No
01-710-1070	Xanomeline High Dose	85	>64	Female	White	No
01-710-1137	Xanomeline High Dose	79	>64	Female	Black or african american	No
01-710-1142	Xanomeline High Dose	76	>64	Female	White	No
01-710-1187	Xanomeline High Dose	78	>64	Female	White	Yes
01-710-1249	Xanomeline High Dose	79	>64	Male	White	Yes
01-710-1278	Xanomeline High Dose	81	>64	Male	White	No
01-710-1354	Xanomeline High Dose	73	>64	Male	White	Yes
01-710-1408	Xanomeline High Dose	80	>64	Male	White	Yes
01-711-1012	Xanomeline High Dose	67	>64	Female	White	No
01-711-1433	Xanomeline High Dose	84	>64	Female	White	No
01-713-1106	Xanomeline High Dose	74	>64	Male	White	Yes
01-713-1141	Xanomeline High Dose	79	>64	Male	White	No
01-713-1209	Xanomeline High Dose	77	>64	Female	White	Yes
01-714-1288	Xanomeline High Dose	77	>64	Male	Black or african american	Yes
01-714-1425	Xanomeline High Dose	81	>64	Male	White	No
01-715-1319	Xanomeline High Dose	65	>64	Male	White	No
01-715-1321	Xanomeline High Dose	75	>64	Female	White	No
01-716-1030	Xanomeline High Dose	83	>64	Female	White	No
01-716-1071	Xanomeline High Dose	78	>64	Female	White	No
01-716-1189	Xanomeline High Dose	81	>64	Male	White	No
01-716-1229	Xanomeline High Dose	73	>64	Female	White	No
01-716-1364	Xanomeline High Dose	84	>64	Female	White	Yes
01-716-1373	Xanomeline High Dose	74	>64	Male	White	No
01-716-1418	Xanomeline High Dose	80	>64	Female	White	Yes
01-716-1447	Xanomeline High Dose	72	>64	Female	White	Yes

One row per subject, in treatment group and subject identifier order.

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Subject	Treatment	Age (years)	Age group	Sex	Race	Completed
01-717-1109	Xanomeline High Dose	84	>64	Male	White	Yes
01-717-1174	Xanomeline High Dose	73	>64	Male	White	Yes
01-717-1357	Xanomeline High Dose	77	>64	Male	White	No
01-718-1101	Xanomeline High Dose	82	>64	Male	Black or african american	No
01-718-1328	Xanomeline High Dose	86	>64	Male	White	No
01-718-1371	Xanomeline High Dose	69	>64	Female	White	No
01-718-1427	Xanomeline High Dose	74	>64	Female	Black or african american	No

One row per subject, in treatment group and subject identifier order.

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Listing 16.2.7.1: Serious treatment-emergent adverse events. Safety population.

Subject	Treatment	Preferred term	System organ class	Onset day	Severity	Related	Outcome
01-709-1424	Xanomeline Low Dose	Syncope	Nervous system disorders	5	Moderate	Yes	Recovered/resolved
01-718-1170	Xanomeline Low Dose	Syncope	Nervous system disorders	27	Severe	Yes	Recovered/resolved
01-718-1371	Xanomeline High Dose	Partial seizures with secondary generalisation	Nervous system disorders	38	Severe	No	Recovered/resolved

Onset day is relative to the first dose of study drug. One row per event.

Listing 16.2.8.1: Abnormal laboratory values meeting a liver-injury criterion. Safety population.

Subject	Treatment	Analyte	Visit	Worst post-baseline value	Upper limit of reference range	Multiple of upper limit
01-705-1186	Placebo	Alanine Aminotransferase (U/L)	Week 4	107.0	32.0	3.3
01-705-1186	Placebo	Aspartate Aminotransferase (U/L)	Week 4	135.0	34.0	4.0
01-705-1186	Placebo	Bilirubin (umol/L)	Unscheduled 4.1	124.8	21.0	5.9
01-708-1286	Placebo	Alanine Aminotransferase (U/L)	Week 24	124.0	32.0	3.9
01-708-1286	Placebo	Aspartate Aminotransferase (U/L)	Week 24	168.0	34.0	4.9
01-708-1286	Placebo	Bilirubin (umol/L)	Week 16	8.5	21.0	0.4
01-705-1292	Xanomeline Low Dose	Alanine Aminotransferase (U/L)	Week 12	88.0	34.0	2.6
01-705-1292	Xanomeline Low Dose	Aspartate Aminotransferase (U/L)	Week 12	125.0	34.0	3.7
01-705-1292	Xanomeline Low Dose	Bilirubin (umol/L)	Week 24	12.0	21.0	0.6
01-705-1310	Xanomeline High Dose	Alanine Aminotransferase (U/L)	Week 8	129.0	32.0	4.0
01-705-1310	Xanomeline High Dose	Aspartate Aminotransferase (U/L)	Week 8	114.0	34.0	3.4
01-705-1310	Xanomeline High Dose	Bilirubin (umol/L)	Week 8	15.4	21.0	0.7
01-709-1029	Xanomeline High Dose	Alanine Aminotransferase (U/L)	Week 26	18.0	35.0	0.5
01-709-1029	Xanomeline High Dose	Aspartate Aminotransferase (U/L)	Week 24	27.0	36.0	0.8
01-709-1029	Xanomeline High Dose	Bilirubin (umol/L)	Week 20	53.0	21.0	2.5

One row per subject per analyte, showing the worst post-baseline value and its multiple of the upper limit of the reference range. Restricted to the analytes screened in the potential drug-induced liver injury table.

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A.2 Index of outputs

Every table, figure and listing of this report carries the ICH E3 output number that `R/tlf-index.R` holds for it. The index below lists them all, with the ICH E3 section each number belongs to and the population the output was computed on.

Table 14.1.1

Analysis populations. ICH E3 section 14.1. Randomised population.

Table 14.1.2

Subject disposition. ICH E3 section 14.1. Randomised population.

Table 14.1.3

Demographic and baseline characteristics. ICH E3 section 14.1. Randomised population.

Table 14.1.4

Medical history by body system and preferred term. ICH E3 section 14.1. Conditions reported by at least 5% of subjects in any treatment group, randomised population.

Figure 14.1.1

Disposition of subjects from screening to study completion (Schulz et al. 2010). ICH E3 section 14.1.

Table 14.2.1

Time to first dermatologic treatment-emergent adverse event. ICH E3 section 14.2. Intention-to-treat population.

Table 14.2.1.1

Time to first dermatologic treatment-emergent adverse event (supportive analysis). ICH E3 section 14.2. Per-protocol population.

Table 14.2.2

Change from baseline in supine systolic blood pressure at week 24. ICH E3 section 14.2. Safety population.

Figure 14.2.1

Cumulative incidence of the first dermatologic treatment-emergent adverse event, intention-to-treat population. ICH E3 section 14.2.

Figure 14.2.2

Hazard ratio for the primary endpoint by age group and sex, intention-to-treat population. ICH E3 section 14.2.

Figure 14.2.3

Mean supine systolic blood pressure by visit and treatment group, safety population. ICH E3 section 14.2.

Table 14.3.5

Extent of exposure. ICH E3 section 14.3. Safety population.

Table 14.3.6

Prior and concomitant medications by drug class and preferred term. ICH E3 section 14.3. Medications taken by at least 5% of subjects in any treatment group, safety population.

Table 14.3.1.1

Overview of treatment-emergent adverse events. ICH E3 section 14.3.1. Safety population.

Table 14.3.1.2

Treatment-emergent adverse events by system organ class and preferred term. ICH E3 section 14.3.1. Events reported by at least 5% of subjects in any treatment group, safety population.

Table 14.3.1.3

Treatment-emergent adverse events by maximum severity. ICH E3 section 14.3.1. Events reported by at least 5% of subjects in any treatment group, safety population.

Table 14.3.1.4

Treatment-emergent adverse events by relationship to study drug. ICH E3 section 14.3.1. Events reported by at least 5% of subjects in any treatment group, safety population.

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Table 14.3.1.5

Serious treatment-emergent adverse events. ICH E3 section 14.3.1. Safety population.

Table 14.3.4.1

Shift from baseline to worst post-baseline category. ICH E3 section 14.3.4. Alanine aminotransferase, safety population.

Table 14.3.4.2

Shift from baseline to worst post-baseline category. ICH E3 section 14.3.4. Aspartate aminotransferase, safety population.

Table 14.3.4.3

Shift from baseline to worst post-baseline category. ICH E3 section 14.3.4. Bilirubin, safety population.

Table 14.3.4.4

Shift from baseline to worst post-baseline category. ICH E3 section 14.3.4. Creatinine, safety population.

Table 14.3.4.5

Potential drug-induced liver injury. ICH E3 section 14.3.4. Safety population.

Table 14.3.7

Shift from baseline to worst post-baseline category. ICH E3 section 14.3. Systolic blood pressure measured supine, safety population.

Table 14.3.8

Shift from baseline to worst post-baseline category. ICH E3 section 14.3. QTcF interval, safety population.

Listing 16.2.1.1

Subjects who discontinued the study. ICH E3 section 16.2.1. Randomised population.

Listing 16.2.2.1

Subjects who discontinued for a protocol violation. ICH E3 section 16.2.2. Randomised population.

Listing 16.2.4.1

Demographic data. ICH E3 section 16.2.4. Randomised population.

Listing 16.2.7.1

Serious treatment-emergent adverse events. ICH E3 section 16.2.7. Safety population.

Listing 16.2.8.1

Abnormal laboratory values meeting a liver-injury criterion. ICH E3 section 16.2.8. Safety population.

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B Reproducibility

B.1 Source data

The analysis datasets are the CDISC pilot study datasets (study identifier `CDISCPILOT01`) distributed in the `pharmaverseadam` package. `R/00-adam.R` reads those datasets, restricts them to the randomised treatment groups, derives the treatment-emergent flags used throughout the report, and derives the time-to-event dataset with `admiral::derive_param_tte()`.

B.2 Metadata excerpt (define.xml style)

A define.xml documents every submitted dataset and variable: its name, label, data type and, where applicable, the controlled terminology codelist it draws from. Tools such as `metacore` build a validated metadata object from that specification; the excerpt below hand-curates a subset of ADSL variables used in this report in the same shape, without generating or validating a full define.xml.

Metadata excerpt: ADSL variables used in this report

define.xml-style excerpt, hand-curated

Dataset	Variable	Label	Type	Codelist
ADSL	USUBJID	Unique Subject Identifier	text	
ADSL	TRT01P	Planned Treatment for Period 01	text	TRT01P
ADSL	TRT01A	Actual Treatment for Period 01	text	TRT01P
ADSL	AGE	Age	integer	
ADSL	AGEGR1	Pooled Age Group 1	text	AGEGR1
ADSL	SEX	Sex	text	SEX
ADSL	RACE	Race	text	RACE
ADSL	SAFFL	Safety Population Flag	text	NY
ADSL	ITTFL	Intent-To-Treat Population Flag	text	NY
ADSL	PPROTFL	Per-Protocol Population Flag	text	NY
ADSL	COMPFL	Completers Population Flag	text	NY
ADSL	DCSREAS	Reason for Discontinuation from Study	text	
ADSL	TRTDURD	Total Treatment Duration (Days)	integer	

Illustrative excerpt only, covering the ADSL variables referenced elsewhere in this report; not a validated define.xml. `NY` is the CDISC controlled terminology codelist for No/Yes flags.

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B.3 Analysis results traceability

Every summary table in this report is computed by `gtsummary`, which retains the Analysis Results Dataset (ARD) behind each statistic, following the CDISC Analysis Results Data standard. Each table's ARD can be recovered from its table object, and `cards::bind_ard()` combines the ARDs from several tables into a single dataset, which is the mechanism used for quality control of the numbers reported here.

```
disposition_ard ← gtsummary::gather_ard(tlf_disposition(adsl))[[1L]]
demographics_ard ← gtsummary::gather_ard(tlf_demographics(adsl))[[1L]]
ae_overview_ard ← gtsummary::gather_ard(tlf_ae_overview(adae, adsl))[[1L]]

ard ← cards::bind_ard(disposition_ard, demographics_ard, ae_overview_ard, .quiet = TRUE)
head(as.data.frame(ard)[, c("variable", "stat_name", "stat")], 8)
```

```
                   variable stat_name      stat
1 Reason for discontinuation         n         8
```

```
2 Reason for discontinuation         N        28
3 Reason for discontinuation         p 0.2857143
4 Reason for discontinuation         n         9
5 Reason for discontinuation         N        28
6 Reason for discontinuation         p 0.3214286
7 Reason for discontinuation         n         2
8 Reason for discontinuation         N        28
```

The combined ARD traces every statistic back to the table (Table 14.1.2, Table 14.1.3 or Table 14.3.1.1) and variable that produced it:

```
as.data.frame(dplyr::count(ard, variable, name = "n_rows"))
```

```
                                    variable n_rows
1                              ..ard_total_n..      1
2                                         AGE     32
3                                      AGEGR1     36
4                 Any TEAE leading to withdrawal     26
5                    Any TEAE with fatal outcome     26
6                          Any dermatologic TEAE     26
7                          Any drug-related TEAE     26
8                               Any serious TEAE     26
9                                Any severe TEAE     26
10 Any treatment-emergent adverse event (TEAE)     26
11                           Completed the study     26
12                                         Died     26
13                       Discontinued the study     26
14                                       ETHNIC     35
15                                         RACE     45
16                                   Randomised     26
17                    Reason for discontinuation     90
18                                          SEX     36
19                                       TRT01A     12
20                                       TRT01P     12
21                                      TRTDURD     32
22                    Treated (safety population)     26
```

B.4 Session information

Package versions used for this report

Package	Version	Source
dplyr	1.2.1	RSPM
ggplot2	4.0.3	RSPM
gtsummary	2.5.1	RSPM

Key packages are cited in the reference list: admiral (Mancini et al. 2026), gtsummary (Sjoberg et al. 2021), survival (Therneau 2026), ggsurvfit (Sjoberg et al. 2026), gt (Iannone et al. 2026).

B.5 Table shells

Table shells fix column layout, statistics and placeholder text at SAP sign-off, before database lock. The final report differs from the shell only in the numbers, not in structure. The mockup in Table 22 is the pre-lock shell for Table 14.2.1; the populated table in Table 23 is the same table after database lock, reproduced here for direct comparison.

Table 22: Shell for Time to first dermatologic treatment-emergent adverse event. Intention-to-treat population. Pre-database-lock template.

Treatment group	Subjects	Subjects with an event	Median time to event (days)	Hazard ratio (95% CI)	p-value
Placebo	XX	XX (XX.X%)	XXX (XXX, XXX)	Reference	
Xanomeline low dose	XX	XX (XX.X%)	XXX (XXX, XXX)	X.XX (X.XX, X.XX)	X.XXX
Xanomeline high dose	XX	XX (XX.X%)	XXX (XXX, XXX)	X.XX (X.XX, X.XX)	X.XXX

`xx` marks cells populated only after database lock. Column layout and statistics are fixed at SAP sign-off.

Table 23: Populated after database lock. Time to first dermatologic treatment-emergent adverse event. Intention-to-treat population.

Treatment group	Subjects	Subjects with an event	Median time to event (days)	Hazard ratio (95% CI)	p-value
Placebo	86	20 (23.3%)	Not reached	Reference	
Xanomeline Low Dose	84	39 (46.4%)	80 (55, NA)	2.98 (1.73, 5.13)	<0.001
Xanomeline High Dose	84	39 (46.4%)	89 (50, NA)	3.34 (1.94, 5.75)	<0.001

Medians and confidence intervals are Kaplan-Meier estimates. Hazard ratios come from a Cox proportional hazards model with planned treatment as the only covariate and placebo as the reference group. A median is reported as not reached where fewer than half the subjects in the group had an event.

```
quarto_version ← system2("quarto", "--version", stdout = TRUE, stderr = TRUE)
typst_version ← system2("quarto", c("typst", "--version"), stdout = TRUE, stderr = TRUE)

cat(
  "R:     ", R.version.string,
  "\nQuarto:", quarto_version,
  "\nTypst: ", sub("^typst ", "", typst_version)
)
```

```
R:      R version 4.6.1 (2026-06-24)
Quarto: 1.11.1
Typst:  0.15.1 (9dfd3a08)
```

The exact package versions are pinned in `renv.lock`. Running `renv::restore()` followed by `quarto render` reproduces this report from a clean checkout.

C ADaM Reviewer's Guide

This appendix describes the analysis datasets behind this report, in the spirit of a CDISC ADaM Reviewer's Guide (ADRG): each dataset's structure, its key derived variables, and the population flags used to select analysis subsets. It is a narrative companion to the metadata excerpt in Section B, not a substitute for it.

C.1 Dataset overview

Analysis datasets used in this report

Dataset	Structure	Key derived variables
ADSL	One record per subject	TRT01P/TRT01A, SAFFL, ITTFL, PPROTFL, COMPFL, DCSREAS, AGEGR1
ADAE	One record per subject per adverse event	TRTEMFL (subset to TRUE), RELFL, DERMFL
ADCM	One record per subject per medication	CMCLAS, CMDECOD (sentence case for display)
ADEG	One record per subject per ECG parameter per visit	BNRIND, ANRIND (reference-range indicators)
ADEX	One record per subject	AVAL (total exposure days), derived from EX
ADLB	One record per subject per lab test per visit	BNRIND, ANRIND, ANRHI (upper limit of reference range)
ADMH	One record per subject per medical history finding	MHBODSYS, MHDECOD (sentence case for display)
ADTTE	One record per subject per time-to-event parameter	AVAL, CNSR, derived with admiral::derive_param_tte()
ADVS	One record per subject per vital-signs test per visit	BNRIND, ANRIND (reference-range indicators)

All nine datasets derive from the CDISC pilot study (`CDISCPILOT01`) shipped in `pharmaverseadam`, restricted in `R/00-adam.R` to the three randomised treatment arms. Two additions come from outside `pharmaverseadam`: ADTTE is not shipped and is derived from ADSL and ADAE, and the reason for discontinuation is taken from the SDTM disposition domain in `pharmaversesdtm`, because the pilot ADSL does not carry one.

`R/00-adam.R` also writes `data/counts.rds`, holding the number of subjects screened, randomised, treated and completing, and the number excluded from ADTTE. Those counts describe subjects the analysis datasets exclude, so they cannot live in an analysis dataset; keeping them in the same snapshot is what lets the subject flow figure agree with the tables.

C.2 ADSL: Subject-level analysis dataset

ADSL carries one record per randomised subject and the population flags that select analysis subsets throughout this report:

- `SAFFL`: safety population, subjects who received at least one dose of study drug.
- `ITTFL`: intention-to-treat population; every randomised subject is `"Y"`, since all were randomised and dosed. Intention-to-treat analyses count subjects under `TRT01P` regardless of what they actually received.
- `PPROTFL`: per-protocol population, approximated as safety-population completers. The pilot ships no protocol deviation dataset; the only deviation information available is discontinuation for protocol violation, and those subjects are already excluded as non-completers.
- `COMPFL`: completers, derived from `EOSSTT == "COMPLETED"`.
- `DCSREAS`: reason for discontinuation, merged from the SDTM disposition domain and set to missing for subjects who completed, so that the reason rows of the disposition table sum to the discontinuation count.

`TRT01P` and `TRT01A` (planned and actual treatment for period 01) drive the by-treatment columns of this report, and they do not agree for every subject: 12 subjects randomised to the high dose received the low dose. Population, disposition, baseline and efficacy outputs are therefore reported by `TRT01P`, and safety outputs by `TRT01A`, so the group sizes differ between the two families of tables by design.

C.3 ADAE: Adverse events analysis dataset

ADAE is restricted to treatment-emergent events (`TRTEMFL == "Y"`) reported by safety-population subjects. Two flags derived in `R/00-adam.R` are used beyond the standard ADaM variables:

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- `RELFL`: related to study drug, derived from `AEREL %in% c("PROBABLE", "POSSIBLE", "RELATED")`.
- `DERMFL`: dermatologic event, derived from `AEBODSYS == "SKIN AND SUBCUTANEOUS TISSUE DISORDERS"`; this flag identifies the events contributing to the primary endpoint.

C.4 ADCM and ADMH: Concomitant medications and medical history

ADCM carries one record per medication per safety-population subject, summarised by ATC level 1 drug class (`CMCLAS`) and preferred term (`CMDECOD`). Medications the pilot study left uncoded are reported under a single `Uncoded` class rather than dropped.

ADMH carries one record per medical history finding. The primary diagnosis of Alzheimer's disease is recorded once for every subject with no coded body system; it is the indication rather than a medical history finding, so `R/00-adam.R` excludes it. Medical history is a baseline characteristic, so it is summarised on the randomised population by planned treatment.

C.5 ADEX: Exposure analysis dataset

ADEX carries one record per subject with total exposure duration (`AVAL`, parameter `TDURD`), restricted to the safety population. Table 14.3.5 draws directly from this dataset without further derivation.

C.6 ADLB, ADVS and ADEG: Laboratory, vital-signs and ECG analysis datasets

These three share the same structure: one record per subject per test per visit, restricted to the safety population, with a baseline reference-range indicator (`BNRIND`) carried onto every post-baseline record alongside that record's own indicator (`ANRIND`). That shared structure is what lets `R/tlf.R`'s `tlf_shift()` compute the shift-from-baseline tables (Table 14.3.4.1 to Table 14.3.4.4, Table 14.3.7 and Table 14.3.8) identically for all three domains, keyed only by `PARAM`.

ADEG differs in two ways. Its analysis records are averages of replicate readings, so they carry `DTYPE == "AVERAGE"` rather than a missing `DTYPE`, and only the rederived QTcF, QTcB, QTlc, QT, RR and heart-rate parameters carry reference-range indicators; the ECG interpretation parameter does not.

ADLB additionally carries `ANRHI`, the upper limit of the reference range for each record, which is what makes the liver-injury criteria in Table 14.3.4.5 expressible as multiples of that limit.

C.7 ADTTE: Time-to-event analysis dataset

ADTTE is derived, not sourced, since `pharmaverseadam` does not ship a time-to-event dataset for this study. `R/00-adam.R` builds it with `admiral::derive_param_tte()` from two sources:

- An event source, the first dermatologic treatment-emergent adverse event per subject (`ASTDT`, one row per subject via `slice_min()`).
- A censoring source, the subject's last date known to be alive (`LSTALVDT`), for subjects without a qualifying event.

`AVAL` is the resulting time to event in days, and `CNSR` distinguishes events (`0`) from censoring (`1`). Records without a positive `AVAL` are dropped, and the number of subjects that removes is recorded in `data/counts.rds` so the analysis population can be reconciled with the safety population. `TRT01P`, `TRT01A`, `SAFFL`, `PPROTFL`, `AGE`, `AGEGR1` and `SEX` are merged back from ADSL so that the primary and supportive analyses in the primary and secondary endpoints chapter need no further joins.

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