# Life Cycle of Drug
# How this Cycle Works

PhUSE SDE - Hyderabad

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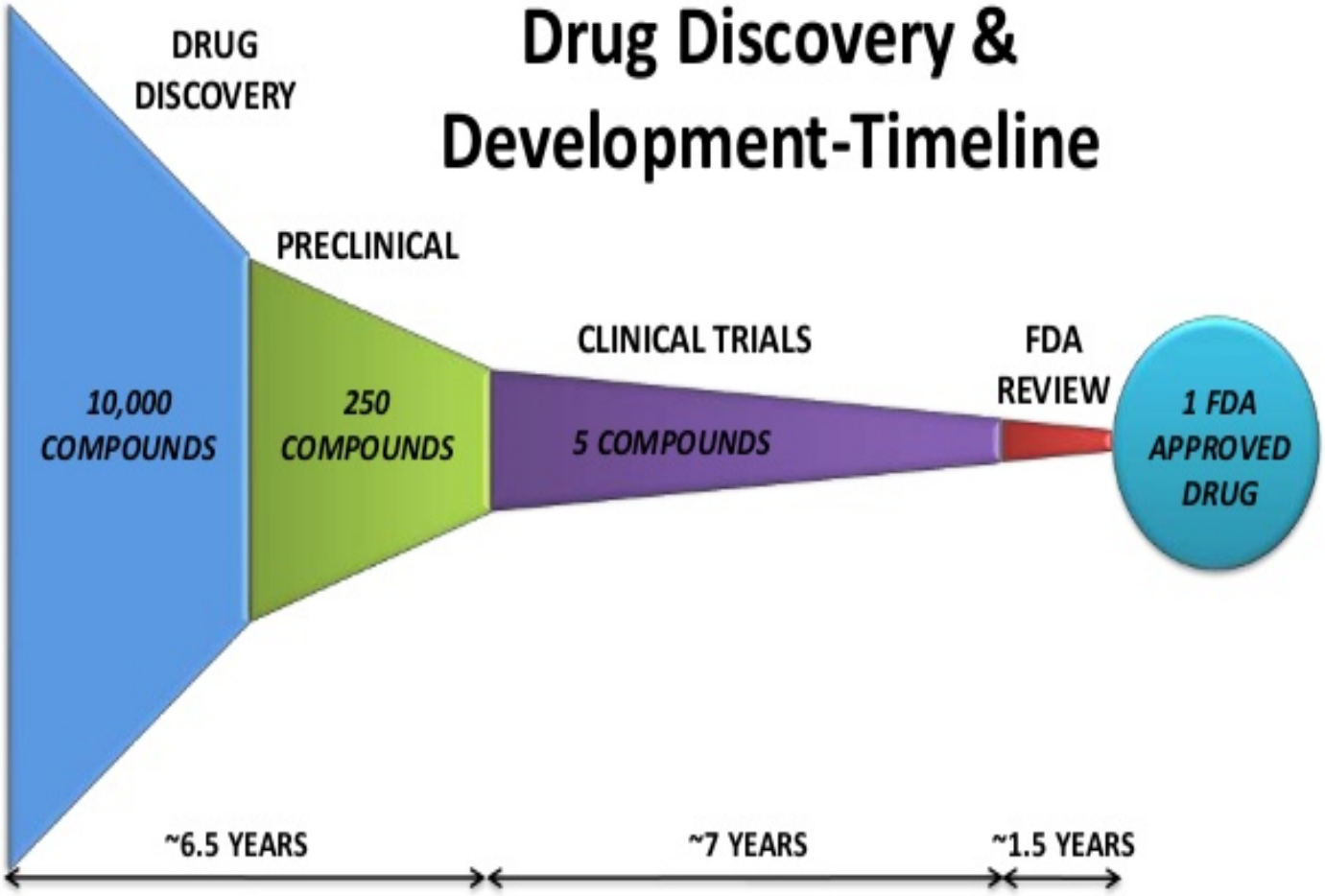
# Agenda

- Introduction to Drug Development & Review
- Clinical Trial Phases
- Role of Statistics & Programming
- Endpoints
- How the Cycle works – Case Study
- Q&A

# Introduction To Drug Development & Review



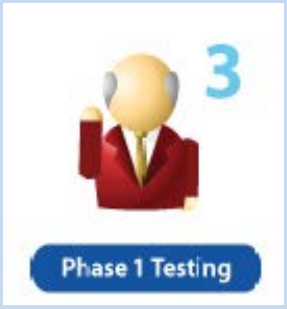
# Introduction To Drug Development & Review

## Background

| R&D Function | Expenditure (%) |
|---|---|
| **Discovery/Basic Research** | |
| Synthesis & Extraction | 10.0 |
| Biological Screening & testing | 14.2 |
| **Preclinical Testing** | |
| Toxicology & Safety Testing | 4.5 |
| Pharmaceutical Dosage Formulation | 7.3 |
| **Clinical Trials** | |
| Phase I,II,III | **29.1** |
| Phase IV | **11.7** |
| Manufacturing & QC | 8.3 |
| IND & NDA | 4.1 |
| Bioavailability & Others | 10.8 |
| **Total** | **100** |

# Introduction To Drug Development & Review Overview










# Clinical Trial Phases
## Overview

| Phases | Dosing | Number Of Subjects | Objectives of Clinical Phase |
|---|---|---|---|
| Preclinical | Unrestricted | Animal testing | Toxicology, Efficacy, Safety |
| 0 | Subtherapeutic | About 10 | PK & PD |
| IA/IB | Ascending dose | 20 – 100 | Dose Ranging |
| IIA/IIB | Therapeutic exploratory | 100 – 300 | Drug Efficacy |
| IIIA/IIIB | Therapeutic confirmatory | 1000 - 2000 | Therapeutic Effect |
| IV | Therapeutic dose | All patients seeking treatment | Long-Term Effects |
| V | No dosing | All reported use | Research on Collected data |

# Role of Statistics

- Statistics is art/science of summarizing data

- At the end of trial, we need outcome to find out
  - Did Treatment work ?
  - Are two groups being compared the same or different ?
  - New method more precise than older ?

- Statistical Inference is the answer

- Statisticians helps to optimize : **Design, Analysis, Interpretation of Results & Conclusion**

# Role of Statistics

**Design**

- Most efficient
- All endpoints of safety & Efficacy
- Which design is most useful
- Sample Size Consideration
- Interim Monitoring Plan
- Assistance in endpoint section

**Analysis**

- Statistical method & Hypothesis for Each endpoint
- Account for Type I & II Error
- Adjustment or stratification
- Handling of missing data
- Subgroup Analysis

# Role of Statistics

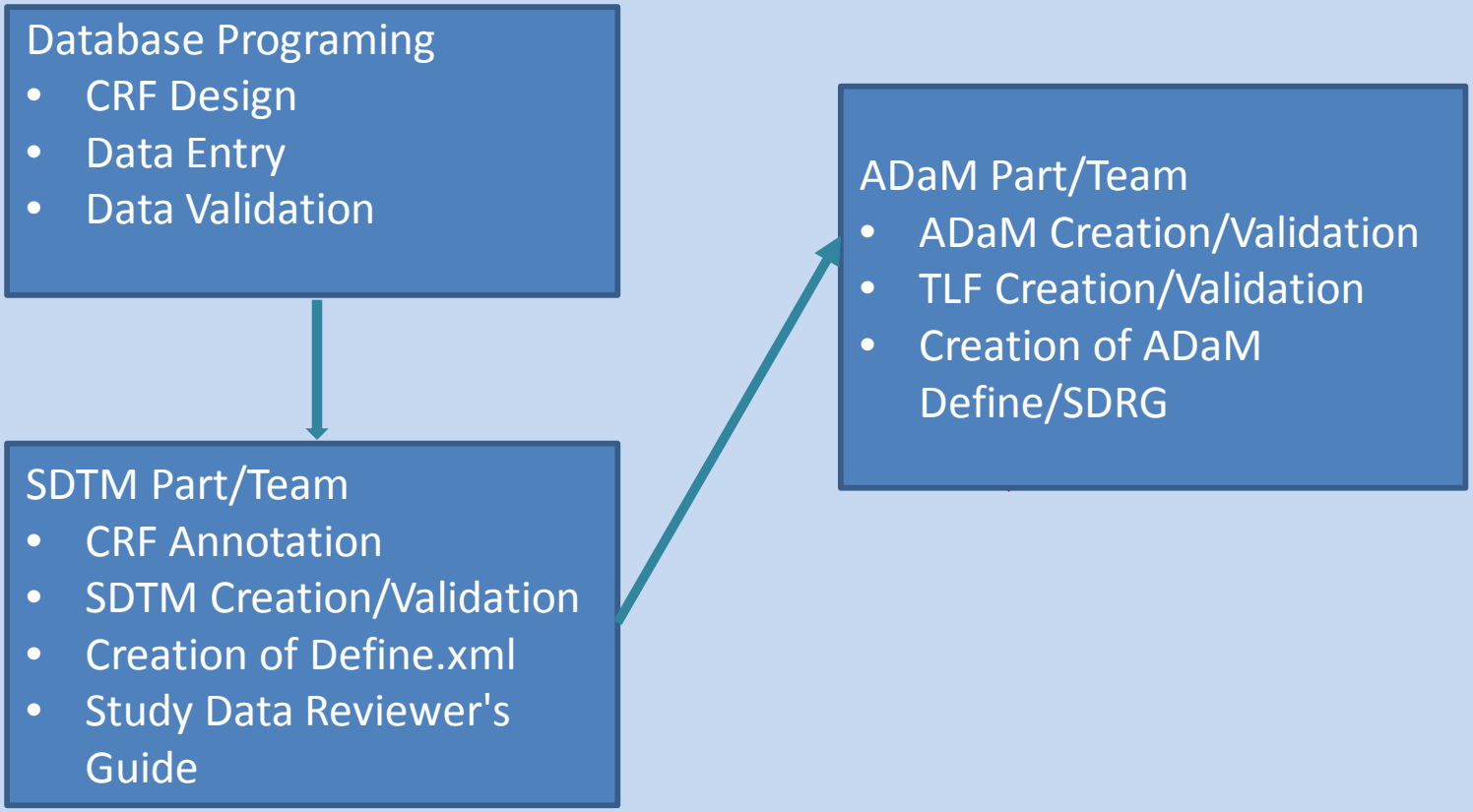
**Interpretations**

- Probability value
- p value is less than 0.05,0.01 & 0.001 then significant
- Hazards Ratio
- Odds Ratio
- Relative Risks

**Conclusion**

- Statistical significance achieved or not
- E.g. Phase 3 study demonstrated that once-daily administration of drug was efficacious for the reduction of xyz in subjects with secondary Hyperthyroidism and Chronic Kidney Disease

# Role of Programing



# Endpoints
## Overview

- What is Clinical Trial Endpoint ?

✓ Measure that allows us to decide whether the null hypothesis of clinical trial should be accepted or rejected

- What is Null Hypothesis ?

✓ No statistically significant difference between two treatments being compared with respects to endpoint measure

- Endpoints composed of Single outcome measure (death) or Combination of outcome measures such as death, hospitalization due to disease

# Endpoints
## Classification

### Primary Endpoint

- ✓ Answer the primary question being asked by a trial for e.g. Reduction in HDL level, New treatment is better at preventing disease related death than standard therapy
- ✓ Sample size based on primary endpoint
- ✓ Statistically significant

### Secondary Endpoint

- ✓ Other relevant questions about same study or trial for e.g. Reduction in disease measure other than death, new treatment reduces overall cost of treating patients
- ✓ Statistical power calculated based on sample size for primary endpoint

# Endpoints

| Types | Example |
|---|---|
| Continuous Measurements | Blood pressures, weight, blood chemistry variables |
| Counts | Frequency of occurrence of migraine headaches |
| Event Times | Time to recurrence of cancer, survival time |
| Binary Endpoints | Major cardiac event yes or no |
| Ordered Categories | Absent, mild moderate, severe pain, NYHA status |
| Unordered Categories | Categories of adverse experiences: GI, cardiac |
| Composite Endpoints | Any non-fatal or fatal allergic reaction |
| Surrogate Endpoints | Reduction in HDL Level, Reduced Ventricular Arrhythmia |
| Economic Endpoints | Quality of life of patients, Cost of care of new treatments |

# Endpoints

## Phase wise Data Analysis

- **Phase I**

✓ Safety evaluated by Treatment Emergent Adverse Events

✓ Drug/Drug Interactions evaluated with TEAEs

✓ Pharmacokinetics evaluated with T1/2, AUC, Cmax, Tmax, etc. variables

✓ Occasional pharmacodynamics or efficacy endpoint evaluated statistically

✓ Statistical methods: largely descriptive

# Endpoints

## Phase wise Data Analysis

- **Phase II**

✓ Survey of clinical endpoints, doses, regimens, etc.

✓ Continued safety evaluation

✓ Statistical methods: rigorous enough to convince yourself result is real

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- **Phase III**

✓ Prospective definition of efficacy on well-defined, regulatory-acceptable, clinical endpoint

✓ Continued safety evaluation

✓ Statistical Methods: rigorous enough to convince the regulators result is real

# Case Study
## Disease

- **Alzheimer's Disease (AD)**

✓ Chronic neurodegenerative disease that usually starts slowly and worsens over period of time

✓ Cause of 60 – 70 % of cases of dementia

✓ Most common early symptom : Difficulty in remembering event
( Short term memory less)

✓ Usual onset : 65 years old  Duration : Long term

# Case Study
## Drug

- **Xanomeline**

✓ Drug(Active Ingredient) used in treatment of Alzheimer's disease

✓ Oral medication has Gastro intestinal side effects which is why new method introduced

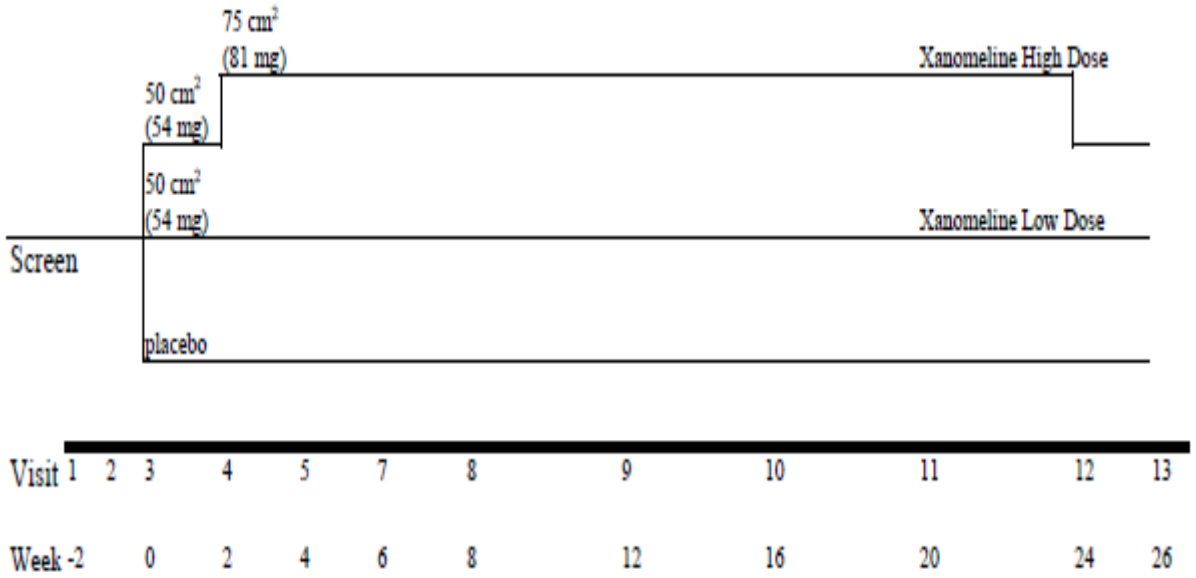
✓ Xanomeline transdermal patches used as medication

✓ Patches provide controlled release of medication into patient

# Case Study

## Trial Design and Plan

- Prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group , phase 2 study.



# Case Study

## Investigational Product

| Treatment Group | Active Ingredient | Total Drug |
|---|---|---|
| Placebo | 0 mg | 0 |
| Xanomeline low dose | 54 mg + small placebo | 54 mg |
| Xanomeline high dose | 54 mg + 27 mg | 81 mg |

| ARMCD | ARM | TAETORD | ETCD | ELEMENT |
|---|---|---|---|---|
| Pbo | Placebo | 1 | SCRN | Screen |
| Pbo | Placebo | 2 | PBO | Placebo |
| Xan_Hi | Xanomeline High Dose | 1 | SCRN | Screen |
| Xan_Hi | Xanomeline High Dose | 2 | HIS | High_Start |
| Xan_Hi | Xanomeline High Dose | 3 | HIM | High_Middle |
| Xan_Hi | Xanomeline High Dose | 4 | HIE | High_End |
| Xan_Lo | Xanomeline Low Dose | 1 | SCRN | Screen |
| Xan_Lo | Xanomeline Low Dose | 2 | LO | Low |

# Case Study
## Endpoints

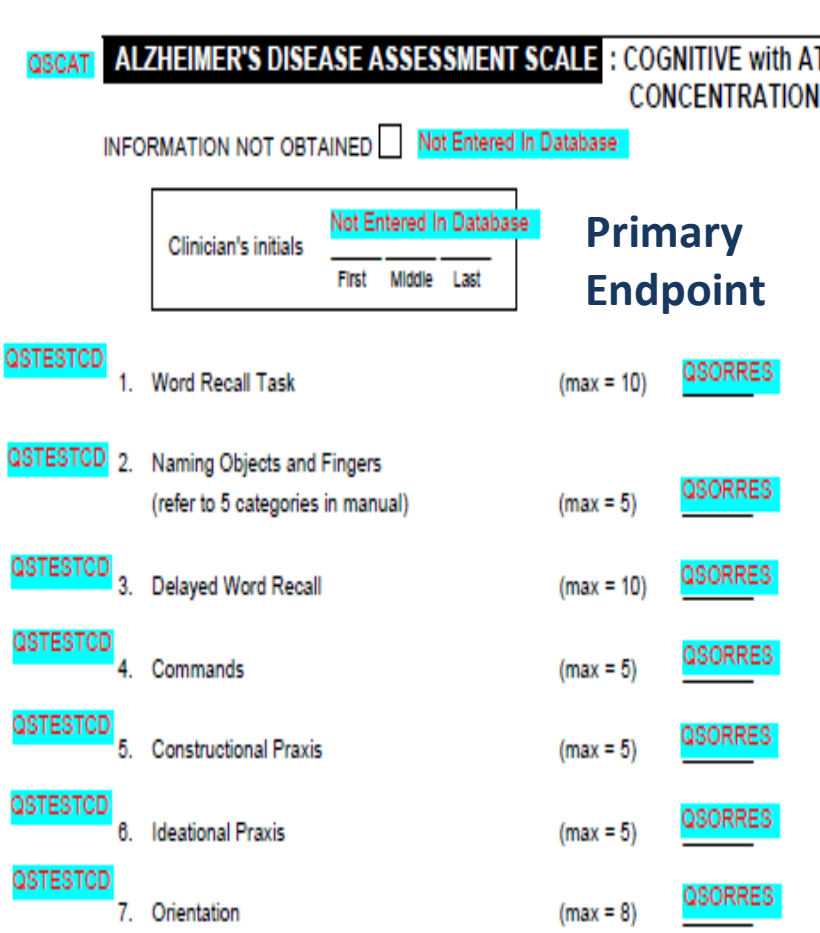
**Primary Endpoints**

- Alzheimer's Disease Assessment Scale - Cognitive Subscale, total of 11 items [ADAS-Cog (11)] at Week 24
- Clinician's Interview-based Impression of Change (CIBIC+) at Week 24

**Secondary Endpoints**

- Alzheimer's Disease Assessment Scale - Cognitive Subscale, total of 11 items [ADAS-Cog (11)] at Weeks 8 and 16
- CIBIC+ at Week 8 and 16
- Mean Revised Neuropsychiatric Inventory (NPI-X) from Week 4 to Week 24

# Case Study
## aCRF



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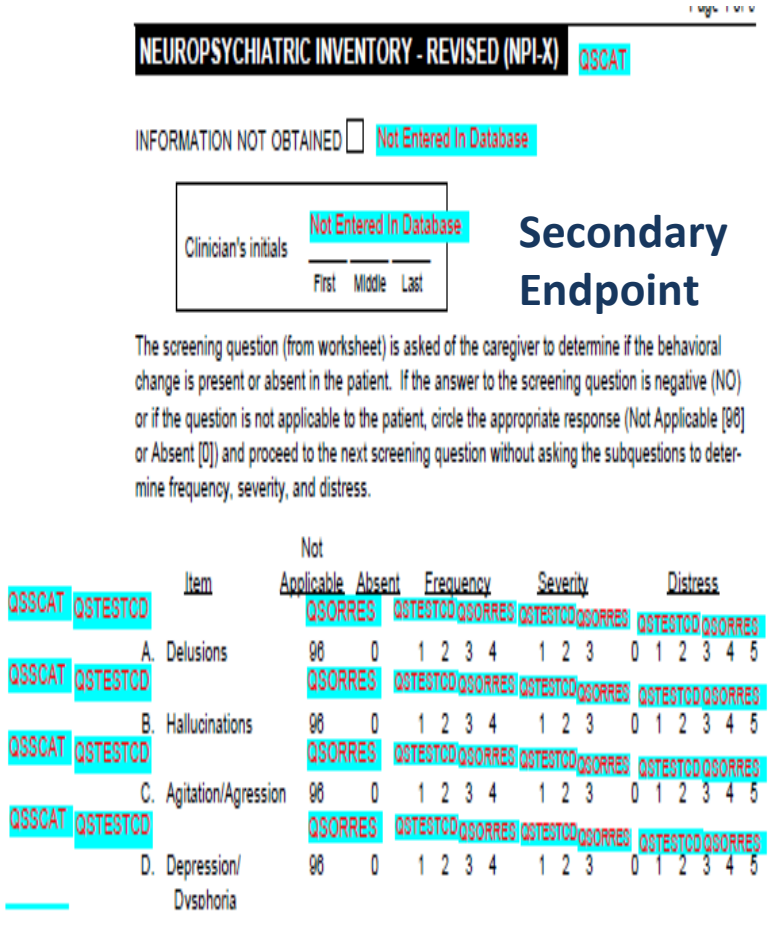
QSCAT **ALZHEIMER'S DISEASE ASSESSMENT SCALE** : COGNITIVE with ATTENTION CONCENTRATION TASKS

INFORMATION NOT OBTAINED ☐ Not Entered In Database

Clinician's initials Not Entered In Database ____ ____ ____ (First Middle Last)

**Primary Endpoint**

| | | | |
|---|---|---|---|
| QSTESTCD | 1. Word Recall Task | (max = 10) | QSORRES |
| QSTESTCD | 2. Naming Objects and Fingers (refer to 5 categories in manual) | (max = 5) | QSORRES |
| QSTESTCD | 3. Delayed Word Recall | (max = 10) | QSORRES |
| QSTESTCD | 4. Commands | (max = 5) | QSORRES |
| QSTESTCD | 5. Constructional Praxis | (max = 5) | QSORRES |
| QSTESTCD | 6. Ideational Praxis | (max = 5) | QSORRES |
| QSTESTCD | 7. Orientation | (max = 8) | QSORRES |



**NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)** QSCAT

INFORMATION NOT OBTAINED ☐ Not Entered In Database

Clinician's initials Not Entered In Database ____ ____ ____ (First Middle Last)

**Secondary Endpoint**

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [98] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

| QSSCAT | QSTESTCD | Item | Not Applicable | Absent | Frequency | Severity | Distress |
|---|---|---|---|---|---|---|---|
| | | | QSORRES | | QSTESTCD QSORRES | QSTESTCD QSORRES | QSTESTCD QSORRES |
| QSSCAT | QSTESTCD | A. Delusions | 98 | 0 | 1 2 3 4 | 1 2 3 | 0 1 2 3 4 5 |
| | | | QSORRES | | QSTESTCD QSORRES | QSTESTCD QSORRES | QSTESTCD QSORRES |
| QSSCAT | QSTESTCD | B. Hallucinations | 98 | 0 | 1 2 3 4 | 1 2 3 | 0 1 2 3 4 5 |
| | | | QSORRES | | QSTESTCD QSORRES | QSTESTCD QSORRES | QSTESTCD QSORRES |
| QSSCAT | QSTESTCD | C. Agitation/Agression | 98 | 0 | 1 2 3 4 | 1 2 3 | 0 1 2 3 4 5 |
| | | | QSORRES | | QSTESTCD QSORRES | QSTESTCD QSORRES | QSTESTCD QSORRES |
| QSSCAT | QSTESTCD | D. Depression/ Dysphoria | 98 | 0 | 1 2 3 4 | 1 2 3 | 0 1 2 3 4 5 |

# Case Study

## SDTM

| Dataset | Description | Class | Structure | Purpose | Keys | Location |
|---|---|---|---|---|---|---|
| TA | Trial Arms | Trial Design | One record per planned Element per Arm | Tabulation | STUDYID, ARMCD, TAETORD | ta.xpt |
| TE | Trial Elements | Trial Design | One record per planned Element | Tabulation | STUDYID, ETCD | te.xpt |
| TI | Trial Inclusion/ Exclusion Criteria | Trial Design | One record per I/E criterion | Tabulation | STUDYID, IETESTCD | ti.xpt |
| TS | Trial Summary | Trial Design | One record per trial summary parameter value | Tabulation | STUDYID, TSPARMCD, TSSEQ | ts.xpt |
| TV | Trial Visits | Trial Design | One record per planned Visit per Arm | Tabulation | STUDYID, VISITNUM | tv.xpt |
| DM | Demographics | Special Purpose | One record per subject | Tabulation | STUDYID, USUBJID | dm.xpt |
| SE | Subject Elements | Special Purpose | One record per actual Element per subject | Tabulation | STUDYID, USUBJID, ETCD | se.xpt |
| SV | Subject Visits | Special Purpose | One record per actual visit per subject | Tabulation | STUDYID, USUBJID, VISITNUM | sv.xpt |
| CM | Concomitant Medications | Interventions | One record per recorded medication occurrence or constant-dosing interval per subject | Tabulation | STUDYID, USUBJID, CMTRT, CMSTDTC | cm.xpt |
| EX | Exposure | Interventions | One record per constant dosing interval per subject | Tabulation | STUDYID, USUBJID, EXTRT, EXSTDTC | ex.xpt |

# Case Study
## ADaM

| Dataset | Description | Class | Structure | Keys |
|---|---|---|---|---|
| ADQSADAS | ADAS-Cog Analysis | BDS | one record per subject per parameter per analysis visit per analysis date | USUBJID, PARAMCD, AVISIT, ADT |
| ADQSCIBC | CIBIC+ Analysis | BDS | one record per subject per parameter per analysis visit per analysis date | USUBJID, PARAMCD, AVISIT, ADT |
| ADQSNPIX | NPI-X Item Analysis Data | BDS | one record per subject per parameter per analysis visit per analysis date | USUBJID, PARAMCD, AVISIT, ADT |
| ADTTE | AE Time To 1st Derm. Event Analysis | BDS | one record per subject per parameter | USUBJID, PARAMCD |
| ADVS | Vital Signs Analysis Dataset | BDS | one record per subject per parameter per analysis visit per analysis timepoint | USUBJID, PARAMCD, AVISIT, ATPT |

# Case Study
## TLFs

**Figure 10-1. Subject Disposition**

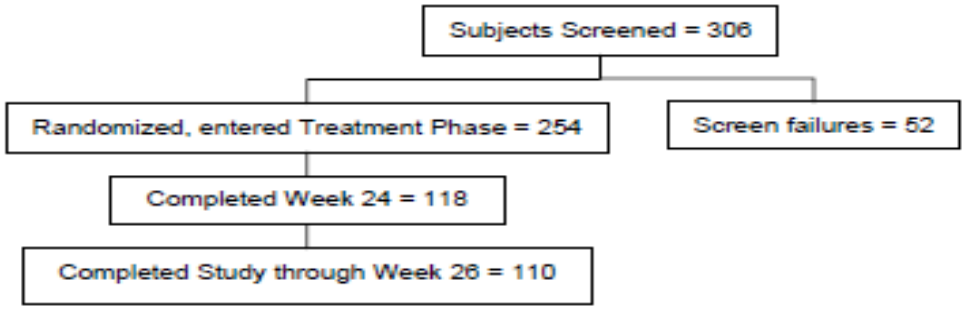



*Table 14-1.01*
*Summary of Populations*

| | Placebo (N=86) | Xanomeline Low Dose (N=84) | Xanomeline High Dose (N=84) | Total (N=254) |
|---|---|---|---|---|
| Intent-To-Treat (ITT) | 86 (100%) | 84 (100%) | 84 (100%) | 254 (100%) |
| Safety | 86 (100%) | 84 (100%) | 84 (100%) | 254 (100%) |
| Efficacy | 79 ( 92%) | 81 ( 96%) | 74 ( 88%) | 234 ( 92%) |
| Complete Week 24 | 60 ( 70%) | 28 ( 33%) | 30 ( 36%) | 118 ( 46%) |
| Complete Study | 58 ( 67%) | 25 ( 30%) | 27 ( 32%) | 110 ( 43%) |

# Case Study
## How Endpoint Derived

Table_14-3.01

| | |
|---|---|
| **Display** | Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population) |
| **AnalysisResult** | **dose response analysis for ADAS-Cog changes from baseline** |
| **Analysis Parameter(s)** | ACTOT=Adas-Cog(11) Subscore |
| **Analysis Variable(s)** | CHG |
| **Reason** | Primary Endpoint Analysis; pre-specified in SAP |
| **Data References (incl. Selection Criteria)** | ADQSADAS[ EFFFL="Y" and ANL01FL="Y" and AVISIT="Week 24" and PARAMCD="ATOT" ] |
| **Documentation** | SAP Section 10.1.1Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose). |
| **Programming Statements** | `proc glm data = ADQSADAS;`<br>`  where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ATOT";`<br>`  class sitegr1;`<br>`  model CHG = trtpn sitegr1;`<br>`run;` |

# Case Study

## Endpoints Establishment

Protocol: CDISCPILOT01 Page 1 of 1
Population: Efficacy

Table 14-3.01

Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF

| | Placebo (N=79) | Xanomeline Low Dose (N=81) | Xanomeline High Dose (N=74) |
|---|---|---|---|
| Baseline | | | |
| n | 79 | 81 | 74 |
| Mean (SD) | 24.1 (12.19) | 24.4 (12.92) | 21.3 (11.74) |
| Median (Range) | 21.0 (5;61) | 21.0 (5;57) | 18.0 (3;57) |
| Week 24 | | | |
| n | 79 | 81 | 74 |
| Mean (SD) | 26.7 (13.79) | 26.4 (13.18) | 22.8 (12.48) |
| Median (Range) | 24.0 (5;62) | 25.0 (6;62) | 20.0 (3;62) |
| Change from Baseline | | | |
| n | 79 | 81 | 74 |
| Mean (SD) | 2.5 (5.80) | 2.0 (5.55) | 1.5 (4.26) |
| Median (Range) | 2.0 (-11;16) | 2.0 (-11;17) | 1.0 (-7;13) |
| p-value(Dose Response) [1][2] | | | 0.245 |
| p-value(Xan - Placebo) [1][3] | | 0.569 | 0.233 |
| Diff of LS Means (SE) | | -0.5 (0.82) | -1.0 (0.84) |
| 95% CI | | (-2.1;1.1) | (-2.7;0.7) |
| p-value(Xan High - Xan Low) [1][3] | | | 0.520 |
| Diff of LS Means (SE) | | | -0.5 (0.84) |
| 95% CI | | | (-2.2;1.1) |

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rtf_eff1.sas 21:05 Monday, June 26, 2006

# Case Study
## How Endpoint Derived

Table_14-3.02

| | |
|---|---|
| **Display** | Table 14-3.02 Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF (Efficacy Population) |
| **AnalysisResult** | **dose response analysis for CIBIC+ values** |
| **Analysis Parameter(s)** | CIBICVAL=CIBIC Score |
| **Analysis Variable(s)** | AVAL |
| **Reason** | Primary Endpoint Analysis; pre-specified in SAP |
| **Data References (incl. Selection Criteria)** | ADQSCIBC[ EFFFL="Y" and ANL01FL="Y" and AVISIT="Week 24" and PARAMCD="CIBICVAL" ] |
| **Documentation** | SAP Section 10.1.1Summary statistics of AVAL at Week 24. Linear model analysis of AVAL for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose); |
| **Programming Statements** | `proc glm data = ADQSCIBC;`<br>`  where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="CIBICVAL";`<br>`  class sitegr1;`<br>`  model AVAL = trtpn sitegr1;`<br>`run;` |

# Case Study

## Endpoints Establishment

*Protocol: CDISCPILOT01* *Page 1 of 1*
*Population: Efficacy*

*Table 14-3.02*
*Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF*

| | Placebo (N=79) | Xanomeline Low Dose (N=81) | Xanomeline High Dose (N=74) |
|---|---|---|---|
| Week 24 | | | |
| n | 79 | 81 | 74 |
| Mean (SD) | 4.3 (0.77) | 4.2 (0.79) | 4.3 (0.81) |
| Median (Range) | 4.0 (2;6) | 4.0 (2;6) | 4.0 (3;6) |
| p-value(Dose Response) [1][2] | | | 0.960 |
| p-value(Xan - Placebo) [1][3] | | 0.489 | 0.799 |
| Diff of LS Means (SE) | | -0.1 (0.13) | 0.0 (0.13) |
| 95% CI | | (-0.3;0.2) | (-0.2;0.3) |
| p-value(Xan High - Xan Low) [1][3] | | | 0.349 |
| Diff of LS Means (SE) | | | 0.1 (0.13) |
| 95% CI | | | (-0.1;0.4) |

P value > 0.05 = No Statistical Significance

# Case Study
## How Endpoint Derived

Table_14-3.12

| | |
|---|---|
| **Display** | Table 14-3.12 Mean NPI-X total score from Weeks 4 through Week 24 - Windowed (Efficacy Population) |
| **AnalysisResult** | **Descriptive statistics (n, mean, standard deviation, median, min, and max)** |
| **Analysis Parameter(s)** | NPTOTMN=Mean NPI-X (9) Total (Week 4 to 24) |
| **Analysis Variable(s)** | AVAL<br>BASE |
| **Reason** | pre-specified in SAP |
| **Data References (incl. Selection Criteria)** | ADQSNPIX[ EFFFL="Y" and PARAMCD="NPTOTMN" and AVISIT="Weeks 4-24" and ANL01FL="Y" ] |
| **Documentation** | SAP Section 10.2 |
| **Programming Statements** | `PROC UNIVARIATE data= ADQSNPIX (where =(EFFFL = 'Y' and PARAMCD = 'NPTOTMN' and AVISIT='Weeks 4-24' and ANL01FL= 'Y'));`<br>` Var BASE AVAL;`<br>` By TRTPN;`<br>`Run;` |

# Case Study
## Conclusion

Protocol: CDISCPILOT01 Page 1 of 1
Population: Efficacy

Table 14-3.12
Mean NPI-X Total Score from Week 4 through Week 24 - Windowed

| | Placebo (N=79) | Xanomeline Low Dose (N=81) | Xanomeline High Dose (N=74) |
|---|---|---|---|
| Baseline | | | |
| n | 79 | 81 | 74 |
| Mean (SD) | 9.5 (12.10) | 8.7 (9.82) | 11.9 (13.70) |
| Median (Range) | 5.0 (0;66) | 4.0 (0;32) | 8.0 (0;61) |
| Mean of Weeks 4-24 | | | |
| n | 78 | 75 | 69 |
| Mean (SD) | 9.3 (11.18) | 9.1 (12.10) | 9.6 (11.60) |
| Median (Range) | 5.5 (0;65) | 3.8 (0;51) | 4.4 (0;46) |
| p-value(Dose Response) [1][2] | | | 0.637 |
| p-value(Xan - Placebo) [1][3] | | 0.760 | 0.517 |
| Diff of LS Means (SE) | | 0.3 (1.13) | -0.7 (1.15) |
| 95% CI | | (-1.9;2.6) | (-3.0;1.5) |
| p-value(Xan High - Xan Low) [1][3] | | | 0.350 |
| Diff of LS Means (SE) | | | -1.1 (1.17) |
| 95% CI | | | (-3.4;1.2) |

# Case Study
## Conclusion

*Protocol: CDISCPILOT01* *Page 1 of 1*
*Population: Intent-to-Treat*

*Table 14-1.02*
*Summary of End of Study Data*

| | Placebo (N=86) | Xanomeline Low Dose (N=84) | Xanomeline High Dose (N=84) | Total (N=254) | p-value[1] |
|---|---|---|---|---|---|
| Completion Status: | | | | | |
| Completed Week 24 | 60 ( 70%) | 28 ( 33%) | 30 ( 36%) | 118 ( 46%) | <.0001 |
| Early Termination (prior to Week 24) | 26 ( 30%) | 56 ( 67%) | 54 ( 64%) | 136 ( 54%) | |
| Missing | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) | |
| Reason for Early Termination (prior to Week 24): | | | | | |
| Adverse Event | 8 ( 9%) | 44 ( 52%) | 39 ( 46%) | 91 ( 36%) | <.0001 |
| Death | 1 ( 1%) | 1 ( 1%) | 0 ( 0%) | 2 ( 1%) | |
| Lack of Efficacy[2] | 3 ( 3%) | 0 ( 0%) | 1 ( 1%) | 4 ( 2%) | 0.3281 |
| Lost to Follow-up | 1 ( 1%) | 0 ( 0%) | 0 ( 0%) | 1 ( 0%) | |
| Subject decided to withdraw | 9 ( 10%) | 8 ( 10%) | 8 ( 10%) | 25 ( 10%) | |
| Physician decided to withdraw subject | 1 ( 1%) | 0 ( 0%) | 2 ( 2%) | 3 ( 1%) | |
| Protocol criteria not met | 1 ( 1%) | 0 ( 0%) | 2 ( 2%) | 3 ( 1%) | |
| Protocol violation | 1 ( 1%) | 1 ( 1%) | 1 ( 1%) | 3 ( 1%) | |
| Sponsor decision | 1 ( 1%) | 2 ( 2%) | 1 ( 1%) | 4 ( 2%) | |
| Missing | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) | |

65% Patients withdrew prematurely from study due to Adverse events

# Case Study
## Conclusion

*Table 14-5.01*
*Incidence of Treatment Emergent Adverse Events by Treatment Group*

| System Organ Class/ Preferred Term | Placebo (N=86) n(%) [AEs] | Xanomeline Low (N=84) n(%) [AEs] | Xanomeline High (N=84) n(%) [AEs] | Fisher's Exact p-values Placebo vs. Low Dose | Fisher's Exact p-values Placebo vs. High Dose |
|---|---|---|---|---|---|
| RESPIRATORY TRACT CONGESTION | 0 | 0 | 1 ( 1.2%) [1] | | 0.494 |
| RHINORRHOEA | 0 | 1 ( 1.2%) [2] | 1 ( 1.2%) [2] | 0.494 | 0.494 |
| DYSPHONIA | 0 | 1 ( 1.2%) [1] | 0 | 0.494 | |
| EMPHYSEMA | 1 ( 1.2%) [1] | 0 | 0 | >0.99 | >0.99 |
| HAEMOPTYSIS | 1 ( 1.2%) [2] | 0 | 0 | >0.99 | >0.99 |
| POSTNASAL DRIP | 1 ( 1.2%) [2] | 0 | 0 | >0.99 | >0.99 |
| RALES | 1 ( 1.2%) [2] | 0 | 0 | >0.99 | >0.99 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 20 (23.3%) [45] | 39 (46.4%) [111] | 40 (47.6%) [104] | 0.002* | 0.001* |
| PRURITUS | 8 ( 9.3%) [11] | 21 (25.0%) [31] | 26 (31.0%) [38] | 0.008* | 0.000* |
| ERYTHEMA | 8 ( 9.3%) [12] | 14 (16.7%) [22] | 14 (16.7%) [22] | 0.175 | 0.175 |
| RASH | 5 ( 5.8%) [9] | 13 (15.5%) [18] | 9 (10.7%) [15] | 0.048* | 0.277 |
| HYPERHIDROSIS | 2 ( 2.3%) [2] | 4 ( 4.8%) [5] | 8 ( 9.5%) [10] | 0.441 | 0.056* |
| SKIN IRRITATION | 3 ( 3.5%) [4] | 6 ( 7.1%) [13] | 5 ( 6.0%) [8] | 0.326 | 0.493 |
| RASH PRURITIC | 0 | 1 ( 1.2%) [2] | 2 ( 2.4%) [3] | 0.494 | 0.243 |
| ACTINIC KERATOSIS | 0 | 0 | 1 ( 1.2%) [1] | | 0.494 |
| BLISTER | 0 | 5 ( 6.0%) [8] | 1 ( 1.2%) [2] | 0.028* | 0.494 |
| PRURITUS GENERALISED | 0 | 1 ( 1.2%) [4] | 1 ( 1.2%) [1] | 0.494 | 0.494 |
| RASH MACULO-PAPULAR | 0 | 0 | 1 ( 1.2%) [1] | | 0.494 |

The main reason for premature withdrawal of patients is skin related adverse events due to transdermal patches

# Case Study
## Conclusion

- A statistically significant dose response was not seen for either of the primary efficacy endpoints: changes from baseline in ADAS-Cog (11) at Week 24 and CIBIC+ at Week 24. Adjusted means for these 2 endpoints were similar for all 3 treatment groups.

- Additional analyses at earlier time points showed similar results. Subgroup analyses by gender, a sensitivity analysis for missing data, and a repeated measures analysis for ADAS-Cog (11) also indicated lack of treatment response.

- The secondary efficacy endpoint of the mean NPI-X values from Week 4 through Week 24 also did not demonstrate a statistically significant dose response.

# References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# Thank You !!


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