

STRIKING A BALANCE:

Adoption of Analysis Results Metadata (ARM) in Early Stage Development (ESD) Studies



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Objectives

Discuss benefit and risks of early adoption

- ✓ Extensive time-retrospective task
- ✓ Pay now or later, regardless of the success of a compound

Share Merck's approach to pilot delivery of an ARM in ESD studies

- ✓ ARM for selected types of ESD studies
- ✓ Proposal for selected CSR output with examples

Acronyms

Acronym	Description
ARM	Analysis Results Metadata
AUC	Area under the curve
C24hr	Concentration in 24 hours
Cmax	Maximum concentration
ESD	Early Stage Development
LSD	Late Stage Development
PD	Pharmacodynamic
PK	Pharmacokinetics
PoC	Proof of concept
PT	Preferred term
QTcF	QTc Fridericia
QTcP	QT corrected population
SOC	System organ class

Agenda

1. Introduction & Background
2. Regulatory Documents & Expectations
3. Contrasting Late and Early Stage ARM Implementation
4. Challenges with ARM Implementation in Early Stage Development
5. General Approach for Creating ARM in ESD Studies
6. Proposal
7. Next Steps
8. Key Takeaways

Introduction & Background

CDISC Analysis Results Metadata Specifications (Released January 2015)

Analysis Results Metadata (Summary) for Study CDISC-Sample

Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population) Dose response analysis for ADAS-Cog changes from baseline Pairwise comparisons to placebo for ADAS-Cog changes from baseline
Table 14-5.02 Incidence of Treatment Emergent Serious Adverse Events by Treatment Group Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

Analysis Results Metadata (Detail) for Study CDISC-Sample

Table 14-3.01

Display	Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Analysis Result	Dose response analysis for ADAS-Cog changes from baseline
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]
Documentation	Linear 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). SAP Section 10.1.1
Programming Statements	[SAS version 9.2] proc glm data = ADQSADAS; where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTFN SITEGR1; run;
Analysis Result	Pairwise comparisons to placebo for ADAS-Cog changes from baseline
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP

Describes the relationship between the key results and the information describing the reason for performing the analysis, the dataset(s), programs and selection criteria(s).

Facilitate the review of the analysis of the primary and key secondary results

Benefit: End-to-end data traceability while giving the reviewers a means to trace results from the displays back to the programs, datasets, statistical analysis plans and supportive documents

Current Regulatory Documents & Expectations

FDA Expectations

- Define-XML version 2.0 required for studies started after December 16, 2016
- Inclusion of the analysis results metadata is still considered optional, but recommended
- Submission of electronic data does not differentiate between early and late stage requirements

PMDA Expectations

- PMDA strongly recommends that sponsors create the ARM for all submissions after March 31, 2020
- PMDA indicates that clinical pharmacology studies include the ARM if it supports the main results of the clinical study using CDISC standard formats.

Rest of World Expectations

- EMEA and China have not required the use of an ARM to-date
- In fact most countries do not require submission of datasets; these countries have not exercised the full potential of study data standards, including ARM

Late Stage Development (LSD) – ARM Implementation

- Highlight primary results in LSD pivotal studies that support safety and efficacy
- Regulatory feedback during stage gates may help guide the selection of outputs documented in ARM
- ADaM requirements introduced the ARM
 - Positive feedback reinforced the value of the ARM in LSD studies
 - Regulatory guidance does not differentiate ARM implementation by study phase

Contrast between ESD and LSD ARM Implementation

Efficacy in ESD

ESD studies may not have a well-defined endpoint like LSD studies

- General objectives involves Pharmacokinetics (PK) and sometimes Pharmacodynamics (PD)
- Different types of studies: Drug-drug Interaction (DDI), First In Human (FIH) [Single Ascending Dose (SAD)/Multiple Ascending Dose(MAD)], Formulation etc.

Safety in ESD

- General safety (includes AE, labs and vitals): No pre-specified Events of Special Interest, AE tiers in safety as they are unknown or too early to define
- Majority of studies conducted in healthy participants versus patients

Challenges with ARM Implementation in ESD Studies

Challenge #1: Time Lapse

- Prolonged time lapse (up to 10 years) between the First In Human study completion and the final submission
- Extensive time-retrospective task

Challenge #2: Fully Outsourced Studies (CRO conducted studies)

- The external partnership may not exist
- Sponsor may not be able to retrieve all information from the past

Challenge #3: Selecting Contents for ESD Studies

- Not efficient to follow the general principle of including all primary and key secondary results
- Pragmatic approach with thoughtful interpretation of regulatory guidance/ feedback to select the content; too many outputs will defeat the purpose of an ARM

General Approach & Proposal

General Approach for Creating ARM in ESD Studies

Include:

- Model-based PK and/or PD analyses related to primary/key secondary objectives/endpoints
- Tables corresponding to hypotheses testing
 - Bayesian or p-value/confidence interval based testing
- Baseline and disposition tables to align with LSD studies
- Limit 1-2 tables supporting safety endpoints (primarily SOC/PT AE table)
 - Proof of concept type studies (with patients) could contain more safety tables

General Approach for Creating ARM in ESD Studies (Cont.)

Exclude:

- Listings and data dumps
- Descriptive summary outputs (PK/PD/Safety labs/ vitals, ECG)
- Tables for exploratory analysis (model-based or descriptive)
- Figures unless it is critical, indispensable and directly linked to the primary endpoint (e.g., Kaplan-Meier plot in oncology studies)

First In Human Single Ascending Dose (SAD) or Multiple Ascending Dose (MAD) Studies

- Baseline Table
- Disposition Table
- PK and/or PD endpoint as primary or key secondary (e.g., C24hr > xx; PD measurement > yy%)
- Safety Table (AE >0% SOC/PT table)

Bioequivalence (BE), Formulation Comparison, Drug-drug (DDI) Interaction Studies

- Baseline Table
- Disposition Table
- Primary Analysis Table (PK parameters: AUC and Cmax comparisons)
- Safety Table (AE >0% Incidence SOC/PT table)

Proposal (Cont.)

QT Studies (TQT)

- Baseline Table
- Disposition Table
- Primary Analysis Table (QTcF comparison table for primary and secondary hypotheses)
- Repeat above if QTcP is appropriate for correction
- Categorical analyses for QTcF (or QTcP if it is appropriate correction)
- Safety Table (AE >0% Incidence SOC/PT table)

ADME Studies

- Baseline Table
- Disposition Table
- Safety Table (AE >0% Incidence SOC/PT table)

Proposal (Cont.)

Proof of Concept (PoC with patients/Phase IB-IIA) Studies

- Baseline Table
- Disposition Table
- Primary and Key Secondary PD Endpoints
- Safety Table (Overall AE Summary)
- Safety Table (AE >0% Incidence SOC/PT)
- Safety Table for Events of Special Interest, if necessary
- Determined as needed

Next Steps & Key Takeaways

Next Steps

- Create a standardized ARM template for major types of ESD studies
- Build-out proposals for other ESD studies (e.g., Concentration-QT studies, Special population studies (Renal or Hepatic))
 - Extend the approach to non-clinical, pre-clinical studies, as appropriate
 - Extend to experimental medicine studies, as appropriate
- Seek regulatory and industry feedback to improvise the current proposal



Microsoft Word
Document

Key Takeaways

- Early adoption of ARM implementation is beneficial regardless of the study phase
- A standardized ARM template offers time-efficient and cost-saving tool in a submission planning
- ESD ARM proposal is a starting point for discussion and first attempt to identify the key analysis in ESD studies that supports product review

References

CDISC Analysis Results Metadata Specifications (Version 1.0) for Define-XML (Version 2.0),
<https://www.cdisc.org/standards/foundational/analysis-data-model-adam/analysis-results-metadata-arm-v10-define-xml-v20>

FDA Study Data Technical Conformance Guide,
<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624623.pdf>

PMDA FAQs on Electronic Study Data Submission (Excerpt),
<http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0007.html#Q512>

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THANK YOU