BIST5092 Phase III Project

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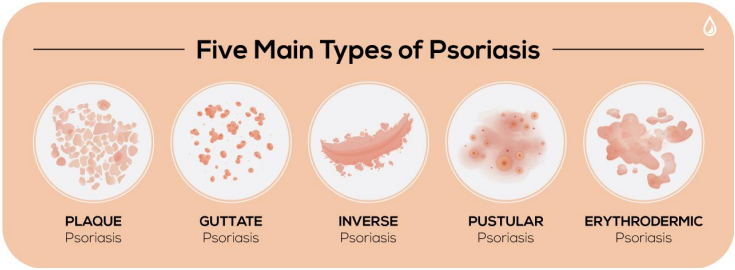
Disclaimer of data: The data is simulated and is not real data from clinical study. They are for educational and exercise purpose only.

Disclaimer: The design of the trial is created based on publicly available open-source information in immunology therapeutic area. It is for educational purpose only. The presentations reflect the views of the speakers based on their understanding of the open source information and simulated data, and have not been evaluated by University of connecticut. The materials cannot be used for promotional activities. They are not intended to diagnose, treat, cure or prevent any disease.

Introduction

A phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of drug X Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis

- Patients with moderate-to-severe plaque psoriasis
- Treatment
  - 210 mg drug X
  - 140 mg drug X
  - Ustekinumab (active control)
  - placebo



Primary objectives

- Superiority of drug X over placebo at week 12 with respect to at least a 75% reduction in the psoriasis area-and-severity index score (PASI 75)
- Static physician's global assessment (sPGA) score of 0 or 1 (clear or almost clear skin)
- Superiority of drug X over ustekinumab at week 12 with respect to a 100% reduction in PASI score (PASI 100)

Study Objectives

The main analysis: analyze treatment effects using the full dataset with logistic regression

A major problem in the analysis of clinical trials is missing data caused by patients dropping out of the study before completion. In submissions with non-negligible amounts of missing data, sensitivity analyses should be presented as support to the main analysis.

The reason for withdrawal :

- study-related (eg, adverse event, death, unpleasant study procedures, lack of improvement)
- study-unrelated (eg, moving away, unrelated disease)

There are three commonly seen missing mechanisms:

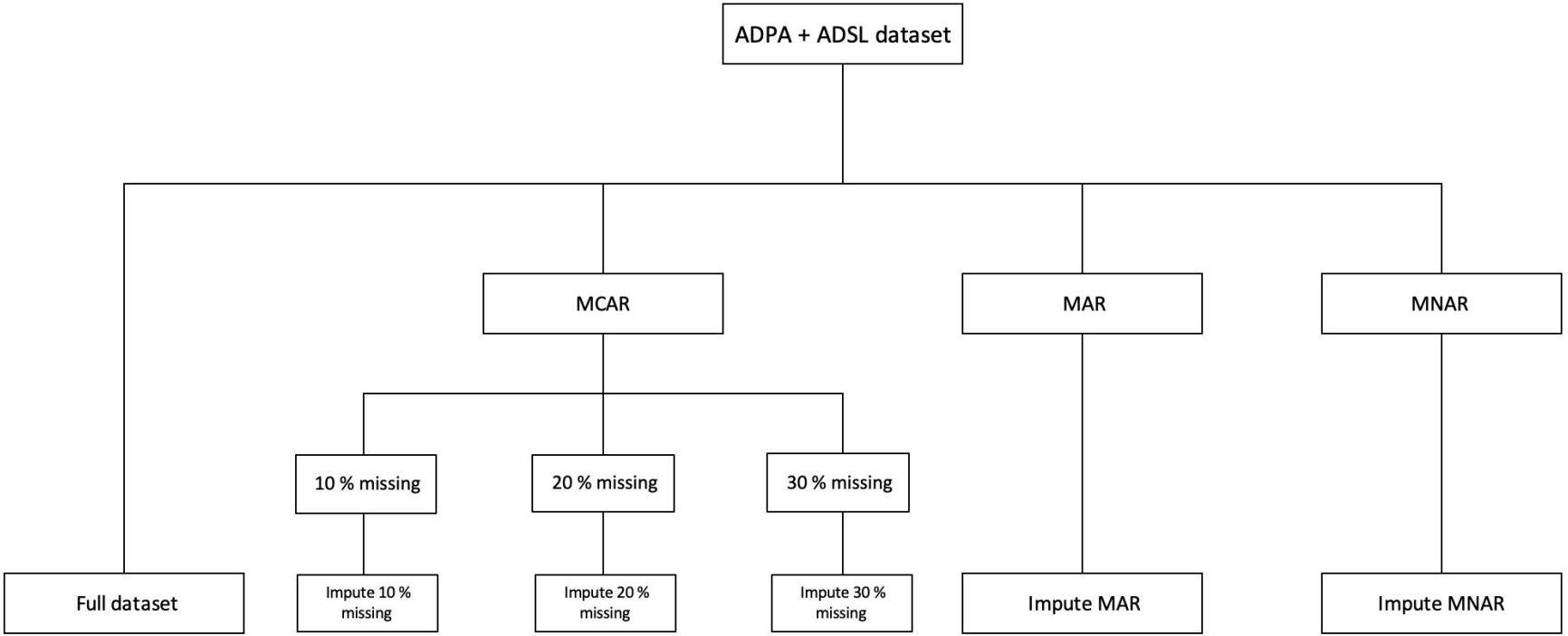
- MCAR (Missing completely at random): The probability of missing is the same for all patients
- MAR (Missing at random): Most missingness is not completely at random
- MNAR (Missing not at random): Missingness that depends on unobserved predictors

Description of Dataset

The simulated dataset contains complete data. It means that every patient has data collected for endpoint at visit 6.

- ADSL (Subject-Level Analysis Dataset)
  - One record per study identifier per subject identifier
  - Key variables
    - STUDYID: Study identifier
    - SUBJID: Subject identifier for the study
    - SEX (confounder): Sex
- ADPA (Efficacy Analysis Dataset)
  - One record per study identifier per subject identifier per parameter code (per analysis visit)
  - Key variables
    - AVISIT: Analysis visit
    - PARAMCD: Parameter code
    - TRTPN (predictor): Planned treatment
    - PCHGCA1N (outcome): Binary indicator of PASI 75
- ADAE (Adverse Event Analysis Dataset)
  - One record per study identifier per subject identifier per adverse event
  - Key variables
    - AESTDY: AE start date relative to the study start date
    - AEENDY: AE end date relative to the study start date
    - AEREL: Investigator's assessment of whether AE is related to the treatment or not
    - AESER: AE serious or not
    - AESEV: AE severity

Data Imputation and Analysis



Data Imputation and Analysis

- Missing Completely at Random (MCAR)
  - Randomly selected 10%, 20% and 30% of the participants to have their visit 6 measurements missing
  - Impute all missing measurements as non-responders (PCHGCA1N = 0)
  - Perform logistic analysis for the primary outcome with treatment and sex for the datasets containing missing values and imputed values
    - PCHGCA1N ~ TRTPN + SEX

Data Imputation and Analysis

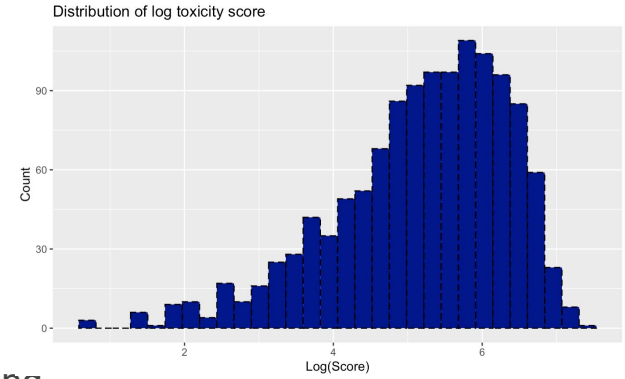
- Missing at Random (MAR)
  - Pattern of missing: patients are more likely to miss later visits if the treatments have little effect
    - If patients has less than 10% improvement (PCHG < 10) on the previous visit, their probability of missing the current visit is 30%, otherwise 5%
    - If one visit has missing measurements, all follow up visits measurements are missing
    - Generate missingness for vist 4, visit 5 and visit 6
  - Impute the missing values by treating them as non-responders (PCHGCA1N = 0)
  - Perform logistic regression on the datasets with missing values and imputed values
    - PCHGCA1N ~ TRTPN + SEX

Data Imputation and Analysis

- Missing Not at Random (MNAR)
  - Generate missingness based on the ADAE dataset
    - Duration of the adverse event = AEENDY - AESTDY
    - Severity score calculated based on if the adverse event is treatment related (AEREL, Y = 1), whether the adverse event is serious (AESER, Y = 1), and the severity of it (AESEV, Mild = 1, Moderate = 2, Severe = 3)
      - Severity score = 5 * AEREL + 3 * AESER + 2 * AESEV
    - Toxicity score = Duration of the adverse event * Severity score
      - Sum multiple toxicity scores for one subject

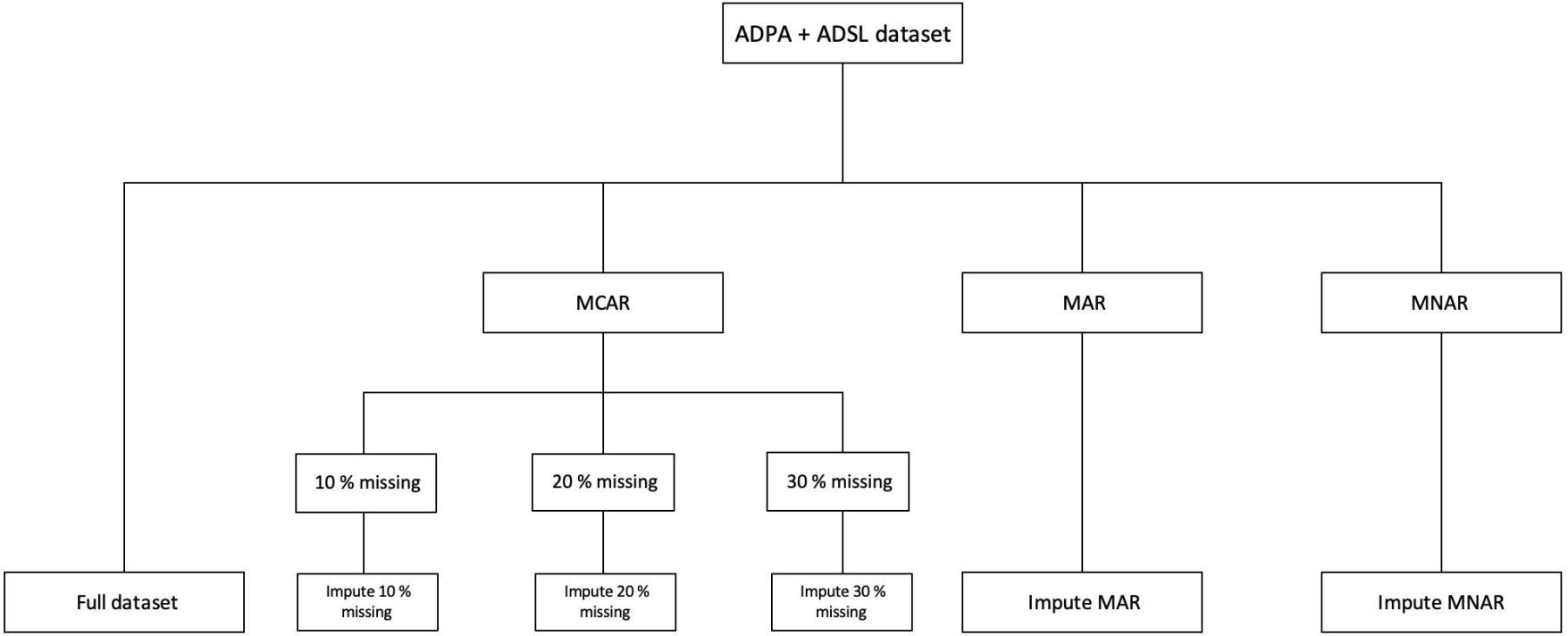
1	USUBJID	AESEQ	AESTDY	AEENDY	AESER	AESEV	AEREL	AEOUT	ARM
2	2012_0103-0003	1	13	84	N	MILD	Y	RECOVERIN(	Placebo
3	2012_0103-0003	2	55	84	N	SEVERE	N	RECOVERIN(	Placebo

Data Imputation and Analysis



- Missing Not at Random (MNAR)
  - Generate missingness based on the ADAE dataset
    - Transfer the toxicity score into the probability of missing
      - Assume the probability of missing is positively related to the toxicity score
      - The original toxicity score is extremely skewed, so we take a log transformation
      - Assume the log toxicity score is normally distributed with mean = mean of log toxicity score, standard deviation = sd of log toxicity score + 1 ~ $N(5.1, 2.17^2)$
      - Simulated probabilities: 0.019 to 0.85, mean = 0.5
      - Impute the missingness with the probability from the previous step
  - Impute the missing values by treating them as non-responders (PCHGCA1N = 0)
  - Perform logistic regression on the datasets with missing values and imputed values
    - PCHGCA1N ~ TRTPN + SEX

Data Imputation and Analysis



Results

Model number	Model Description	Active control	140 mg	210 mg	Sex Male	
		log(OR)	log(OR)	log(OR)	log(OR)	p-value
1	Full dataset	3.2724	3.1169	4.2609	0.194	0.117
2	MCAR 10%	3.1982	3.062	4.1797	0.156	0.234
3	MCAR 20%	3.2763	3.154	4.2759	0.1718	0.221
4	MCAR 30%	3.1821	3.1922	4.325	0.2061	0.172
5	MAR	2.8004	2.6614	3.8378	0.235	0.0773
6	MNAR	3.1769	3.184	4.1499	0.222	0.138
7	MCAR 10% imputed	3.0016	2.864	3.7679	0.1499	0.195
8	MCAR 20% imputed	2.8794	2.8523	3.5386	0.1508	0.176
9	MCAR 30% imputed	2.6584	2.669	3.3617	0.1022	0.353
10	MAR imputed	3.0741	2.9271	3.9604	0.2029	0.0801
11	MNAR imputed	2.3862	2.5904	2.8242	0.0561	0.605

* p-value of all treatmentment effects from all models are significant $p < 2$ e-16

Summary

- Key findings:
  - Compared to patients taking placebo, the odds for patients taking active control (ustekinumab), 140mg, and 210mg of drug X to reach at least 75% skin clearance are 26.37, 22.57, and 70.87 times accordingly, after adjusted for a potential confounder sex.
  - The primary findings are endorsed by sensitivity analysis in which we knocked out certain percentages of the data by all three proposed mechanisms of missing. In the worst case scenario where all missing data are assigned the worst treatment value, the treatment effects are still significant.
- To conclude, this study proved the efficacy of drug X on clearing the skin conditions of psoriasis patients with proposed dosage against placebo, which is also endorsed by the sensitivity analysis.