A Practical Implementation of Multiple Imputations for Analysis of Long-Term Categorical Outcomes From Ixekizumab UNCOVER-3 Study

Lu Zhang

Eli Lilly and Company, Indianapolis, IN, USA

24th Annual Biopharmaceutical Applied Statistics Symposium

October 23, 2017

This study was sponsored by Eli Lilly and Company.

Disclosures

- **Lu Zhang** is an employee and stockholder of Eli Lilly and Company
- This study was sponsored by Eli Lilly and Company

Background

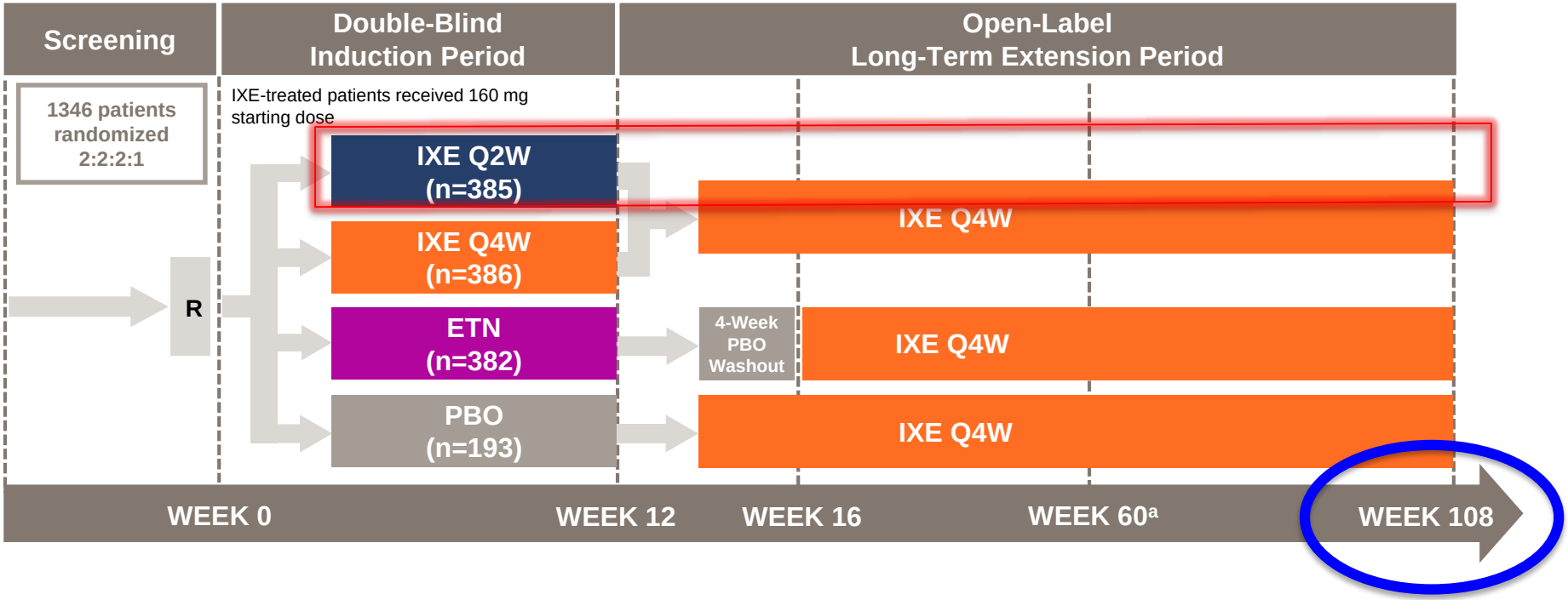
- Analyzing long-term efficacy outcomes can be particularly challenging because the rate of discontinuation from a study can only increase with time, presenting the problem of missing data
- The use of different methods for handling missing data has implications for different clinical questions[1], thus suggesting the need for different estimands
- Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A[2-4]
  - Approved for treating moderate-to-severe plaque psoriasis
  - UNCOVER-3 includes a long-term extension of ixekizumab up to ~5 years

1. Langley RG et al. *J Drugs Dermatol* 2017;16:734-741
2. Griffiths CE et al. *Lancet* 2015;386:541-51
3. Gordon KB et al. *N Engl J Med* 2016;375:345-56
4. Blauvelt A et al. *J Am Acad Dermatol* 2017;(Ahead of print)

Objective

- To examine how different methods of handling missing data can influence the efficacy response rates of ixekizumab in UNCOVER-3

Study Design



[a] After Week 60, patients could increase dosage to IXE Q2W until the end of the study at the investigator's discretion

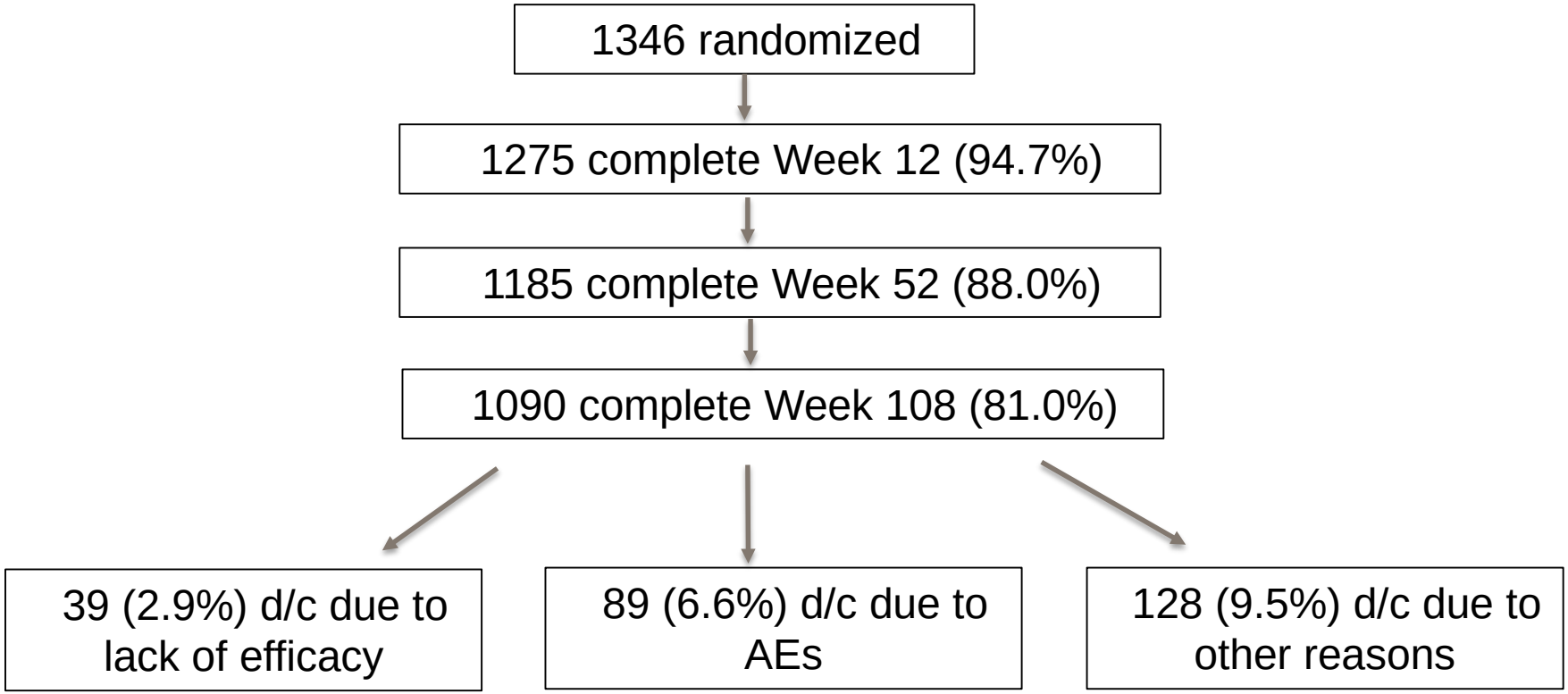
ETN=50 mg etanercept twice weekly; IXE Q2W=80 mg ixekizumab every 2 weeks; IXE Q4W=80 mg ixekizumab every 2 weeks; PBO=placebo; R=randomization

Efficacy Measures

- Co-primary:
  - At least 75% improvement from baseline on the Psoriasis Area and Severity Index (PASI)
  - Static Physician's Global Assessment (sPGA) score of 0,1
- PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling, redness, and plaque thickness in each region, yielding an overall score of 0 (no psoriasis) to 72 (most severe disease)[5]
- sPGA[6] measures severity of illness at each specific time point using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), very severe (5)

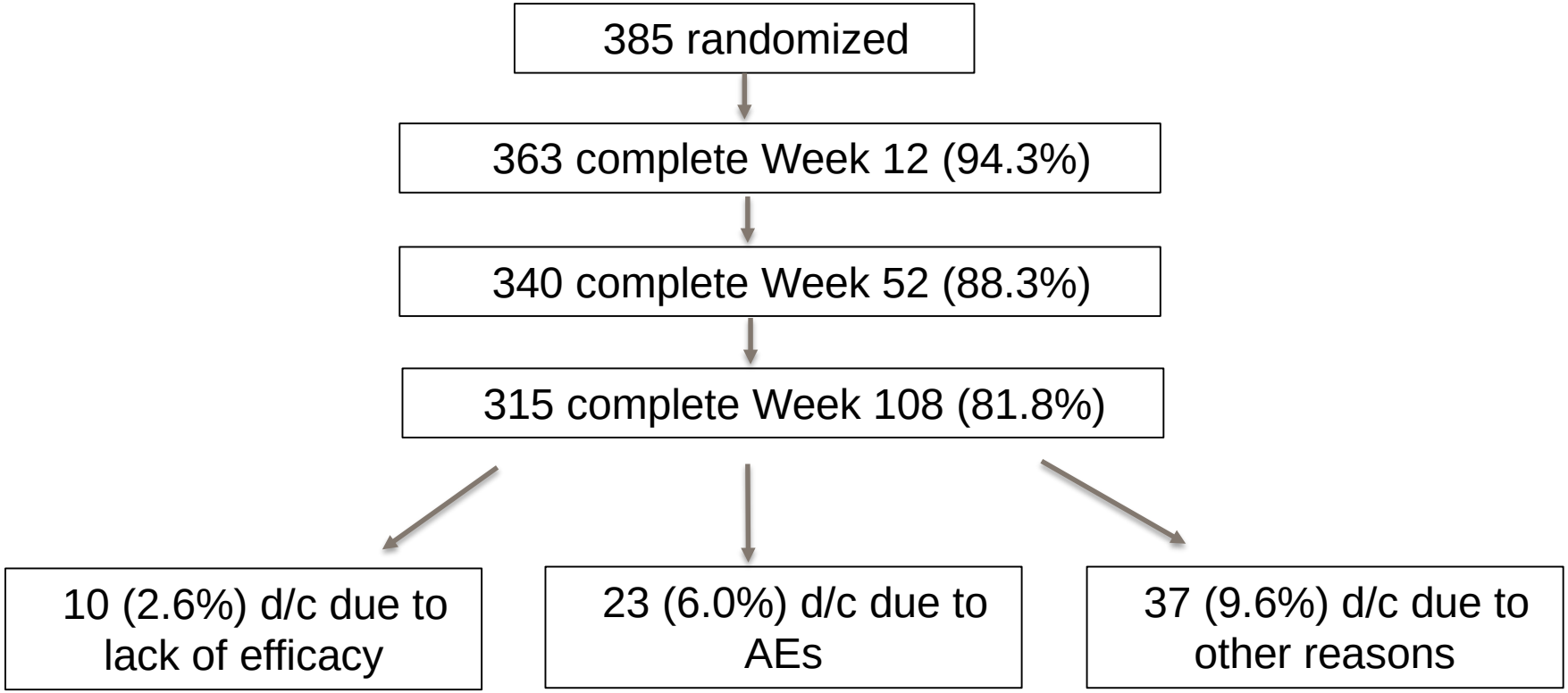
5. Fredriksson T and Pettersson U. *Dermatologica* 1978;157:238-44
6. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf

Discontinuation: Overall Treatments



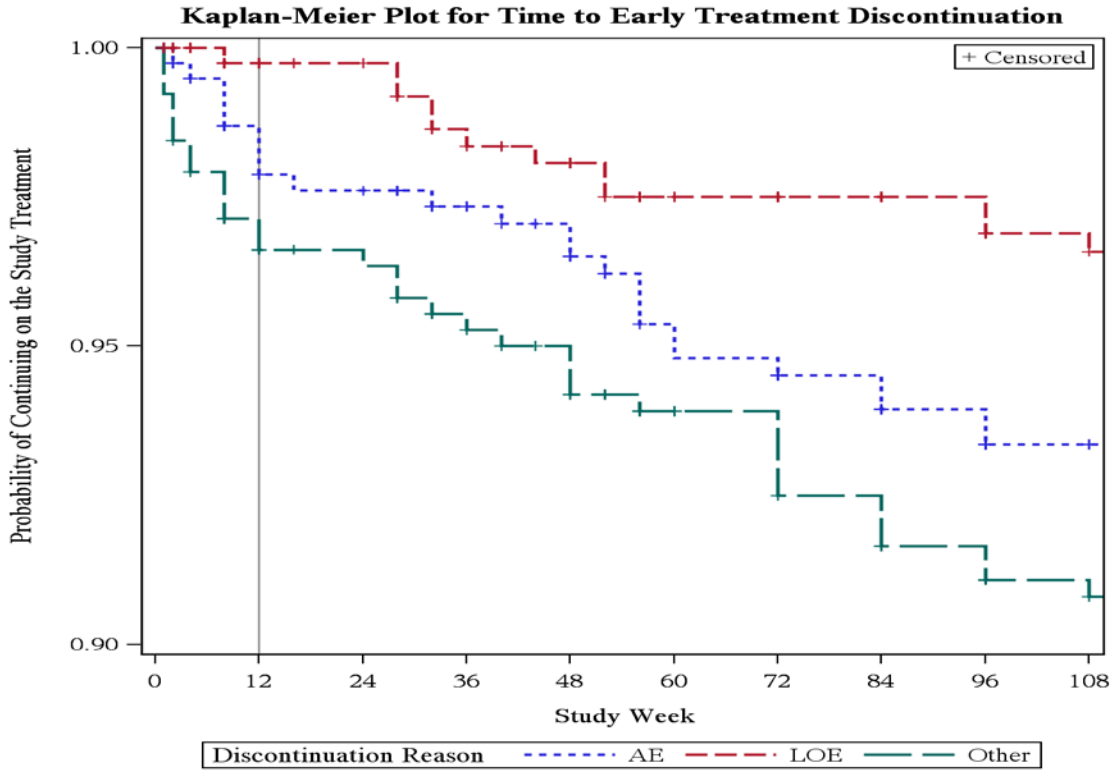
d/c=discontinued; AE=adverse event

Discontinuation: 80 mg Ixekizumab Q2W/Q4W



d/c=discontinued; AE=adverse event

Early Discontinuations: Kaplan-Meier Plot Over Time, 80 mg Ixekizumab Q2W/Q4W



AE=adverse event; LOE=lack of efficacy

Estimands and Definitions

Esti-mand	Population Level Summary	Clinical Outcome	Time Point/ Period	Treatment	Conditions Under Which Treatment Effect Is Evaluated	Population
1	Proportion of subjects with	eg, sPGA(0,1) response (yes/no)	at Visit K	due to study treatment	if taken as directed	in all RDB-ITT subjects
2			at Visit K	due to study treatment	if taken as directed until contraindicated	in all RDB-ITT subjects
3			at Visit K or end of treatment, whichever comes first	due to study treatment	if taken as directed	in all RDB-ITT subjects
4			at Visit K	due to study treatment	if taken as directed	in a subset of RDB-ITT subjects who actually take treatment as directed through Visit K

RDB-ITT=randomized double-blind intent-to-treat; sPGA=static Physician's Global Assessment

Data Considerations for Estimand

Estimand	Usable Data to Be Collected	Data That May Be Missing
1	Data collected while the subjects receive study treatment as intended	Outcomes after start of nonadherence; intermittently missing values
2	Data collected while the subjects receive study treatment as intended and the primary reason for treatment nonadherence	Outcomes after start of nonadherence due to reasons other than treatment contraindication; intermittently missing values
3	Data collected while the subjects receive study treatment as intended	Intermittently missing values
4	Completion status and data collected from completers as they receive study treatment as intended	Intermittently missing values

Imputation Methods

Estimand	Method	Definition
1	MI MCMC	Multiple imputation (MI) of numeric sPGA score using the MCMC method
1	MI REG	MI of numeric sPGA score using sequential regression at all visits
1	MI LOG	MI of binary sPGA(0,1) response status using sequential logistic regression at all visits
1	MI REGLOG	MI of numeric sPGA score using sequential regression at all but the last visits and logistic regression of the binary sPGA(0,1) responder status at the last visit
1	MI PMM	MI of numeric sPGA score using sequential predictive mean matching at all visits
2 (variant 1)	NRI	Nonresponder imputation for all early discontinuations
2 (variant 2)	mNRI	Nonresponder imputation for early discontinuations due to adverse events and lack of efficacy + MI PMM for subjects discontinued due to other reasons
4	OC	Observed data in completers at each visit

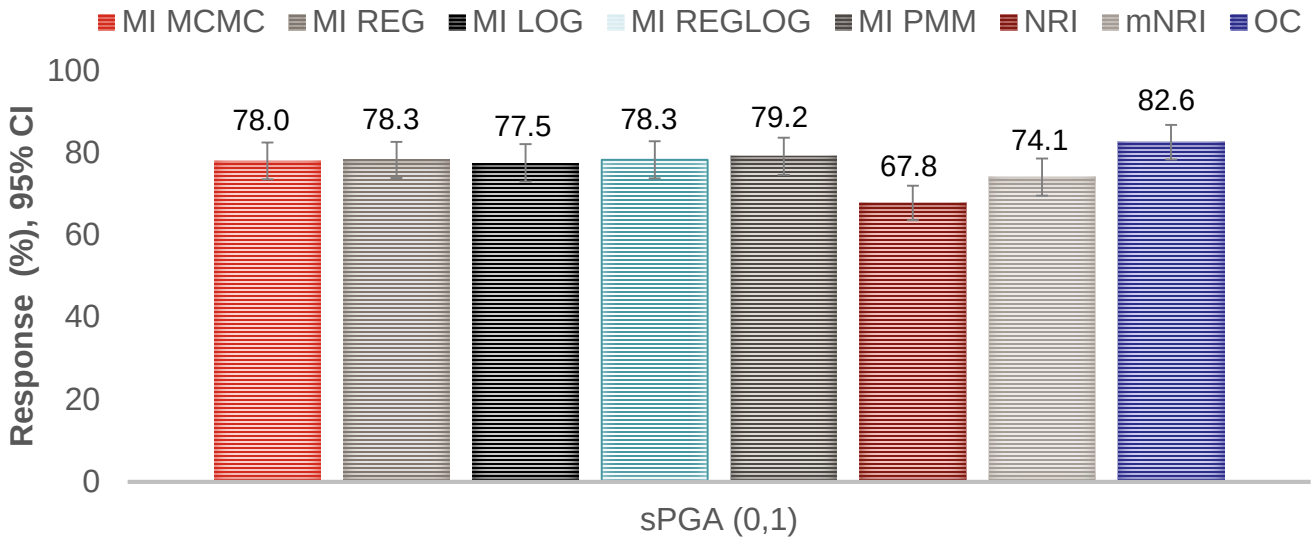
sPGA(0,1) Response Rates at Week 108

Estimand	Method	IXE Q2W/Q4W, % (95% CI) n=385
1	MI MCMC	78.0 (73.6-82.5)
1	MI REG	78.3 (73.9-82.7)
1	MI LOG	77.5 (73.0-82.1)
1	MI REGLOG	78.3 (73.8-82.8)
1	MI PMM	79.2 (74.8-83.5)
2 (variant 1)	NRI	67.8 (63.1-72.5)
2 (variant 2)	mNRI	74.1 (69.6-78.6)
4	OC	82.6 (78.4-86.8) [261/316][a]

[a]Observed counts are shown in brackets

sPGA(0,1) Response Rates at Week 108
80 mg Ixekizumab Q2W/Q4W

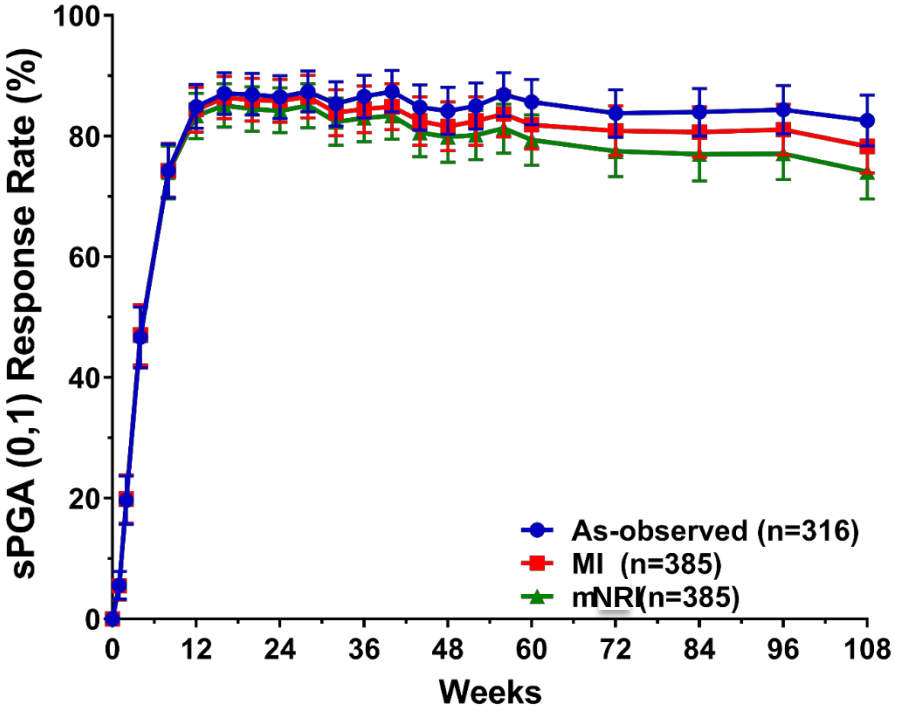
- Similar results were observed with Estimand 1 regardless of different MI methods
- The most conservative analysis, Estimand 2 with the NRI method, gives the lowest response rates, whereas the mNRI result is between those from Estimand 1 and NRI
- Estimand 4, the observed cases/completers analysis, yielded the highest response rates

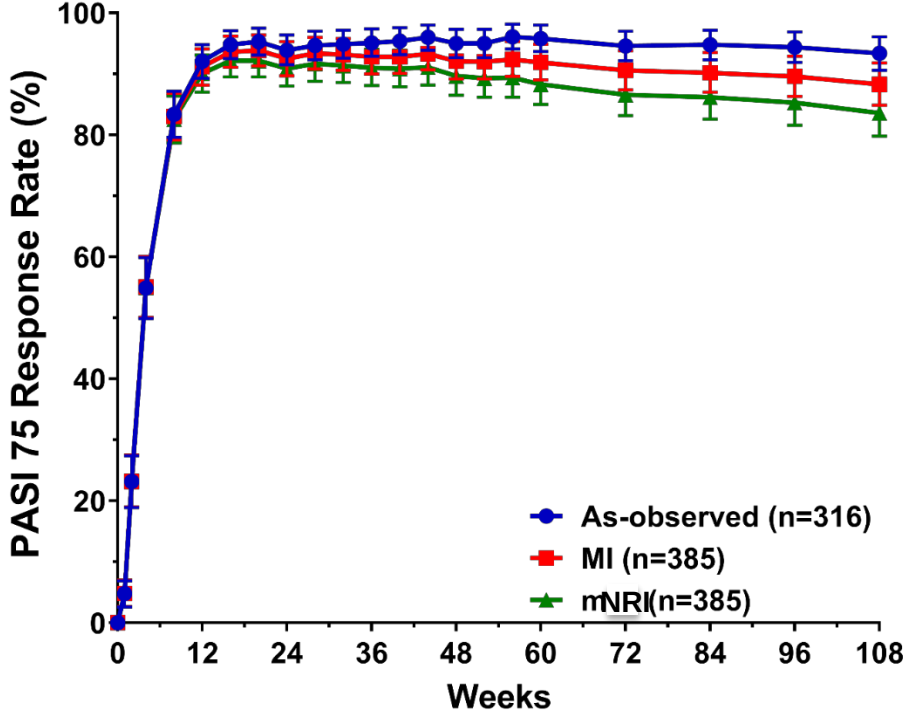


Error bars represent 95% CI

Time Course of sPGA(0,1) & PASI 75 Over 2 Years
80 mg Ixekizumab Q2W/Q4W

The methods presented are as-observed, MI, and mNRI[4]





sPGA=static Physician's Global Assessment; PASI=Psoriasis Area and Severity Index; MI=multiple imputation; mNRI=modified nonresponder imputation

Conclusion

- Regardless of the methods used for handling missing data, patients treated with ixekizumab demonstrated a persistent high level of efficacy responses over time
- The different methods of imputation provide insight into the bias of treatment adherence