European Statistical Meeting:
Advances in the Treatment of Missing Data

Evaluating Handling of Missing Data: Case Study in Diabetes

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Disclosures

Mark Donovan is an Employee of Bristol-Myers Squibb

Saxagliptin is developed by Bristol-Myers Squibb and AstraZeneca

Clinical trial data presentations consist of information from publicly available sources

Summary of Phase 3 Clinical Program

T2DM Oral Anti-diabetic Program

6 Pivotal Phase 3 Clinical Studies

- Two monotherapy
- Three add-on combination
  - MET
  - TZD
  - SU
- One initial combination with metformin

Inclusion Criteria

- A1C:

Monotherapy / Add-on MET	7 – 10%
Add-on TZD	7 – 10.5%
Add-on SU	7.5 – 10%
Initial combination	8 – 12%

Study Designs – Pivotal Phase 3 Studies

- **Randomized, double-blind, controlled, parallel arm, multi-center studies**
- **Placebo lead-in period**
- **24-week short-term period**
- **Controlled long-term extensions blinded to site and subject (12–42 months)**

Study Designs – Pivotal Phase 3 Studies

- **Provision for rescue medication based on pre-specified criteria for lack of efficacy**
  - **Metformin (4 studies) or pioglitazone (2 studies) added as rescue therapy**
- **Once administered, subjects stayed on study, on rescue medication**
- **Based on FPG in ST (FPG > 240 mg/dL → 200 mg/dL)**
- **Based on HbA1c in LT (HbA1c > 8% → 7.5% {7.0%})**
- **Initial high value, confirmed 3-5 days later**

Primary and Common Secondary Endpoints Pivotal Phase 3 Studies

Primary Endpoint

- Change in HbA1c from baseline to Week 24

Secondary Endpoints

- Change from baseline to Week 24 in fasting plasma glucose
- Proportion of patients achieving a therapeutic glycemic response defined as HbA1c < 7% at Week 24
- Change from baseline to Week 24 in the area under the curve from 0 to 180 minutes for postprandial glucose response to an oral glucose tolerance test

Long-term Endpoints

- Change from baseline in HbA1c (& other efficacy variables)

Primary and Common Secondary Endpoints Pivotal Phase 3 Studies

Sample Size Considerations

- Difference 0.35% - 0.7%, S.D. 1.0% - 1.2%
- Expected dropout rates varied, later protocols 5%

Visit Windows

- Scheduled for target day + / - 3 days (LT + / - 7 days)
- Analysis windows: non-overlapping, exhaustive

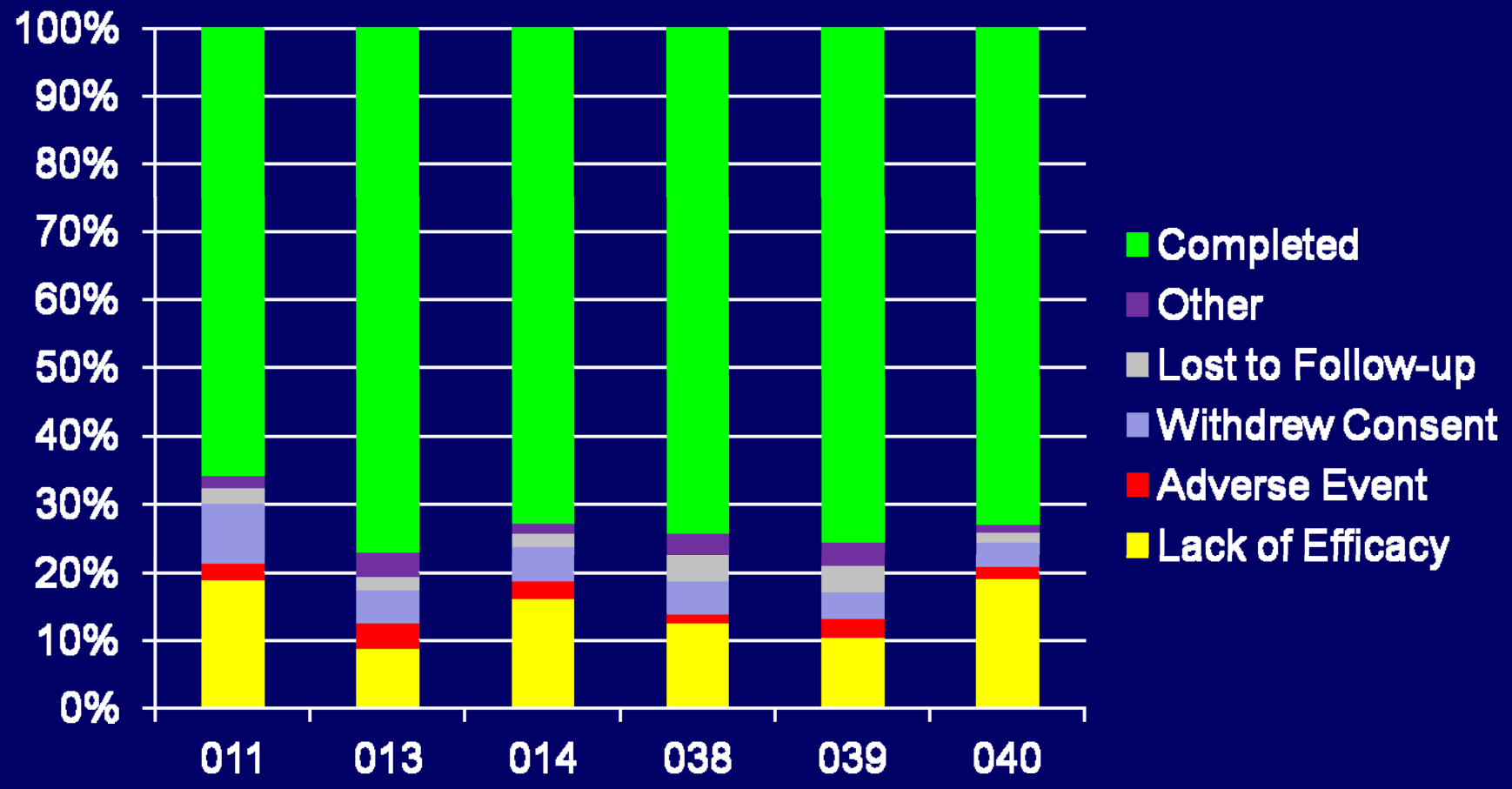
Missing Data

- Primary analysis(ST): LOCF
- Alternative analyses: repeated measures, observed
- Efficacy endpoints included data prior to initiation of rescue therapy
- LT: repeated measures

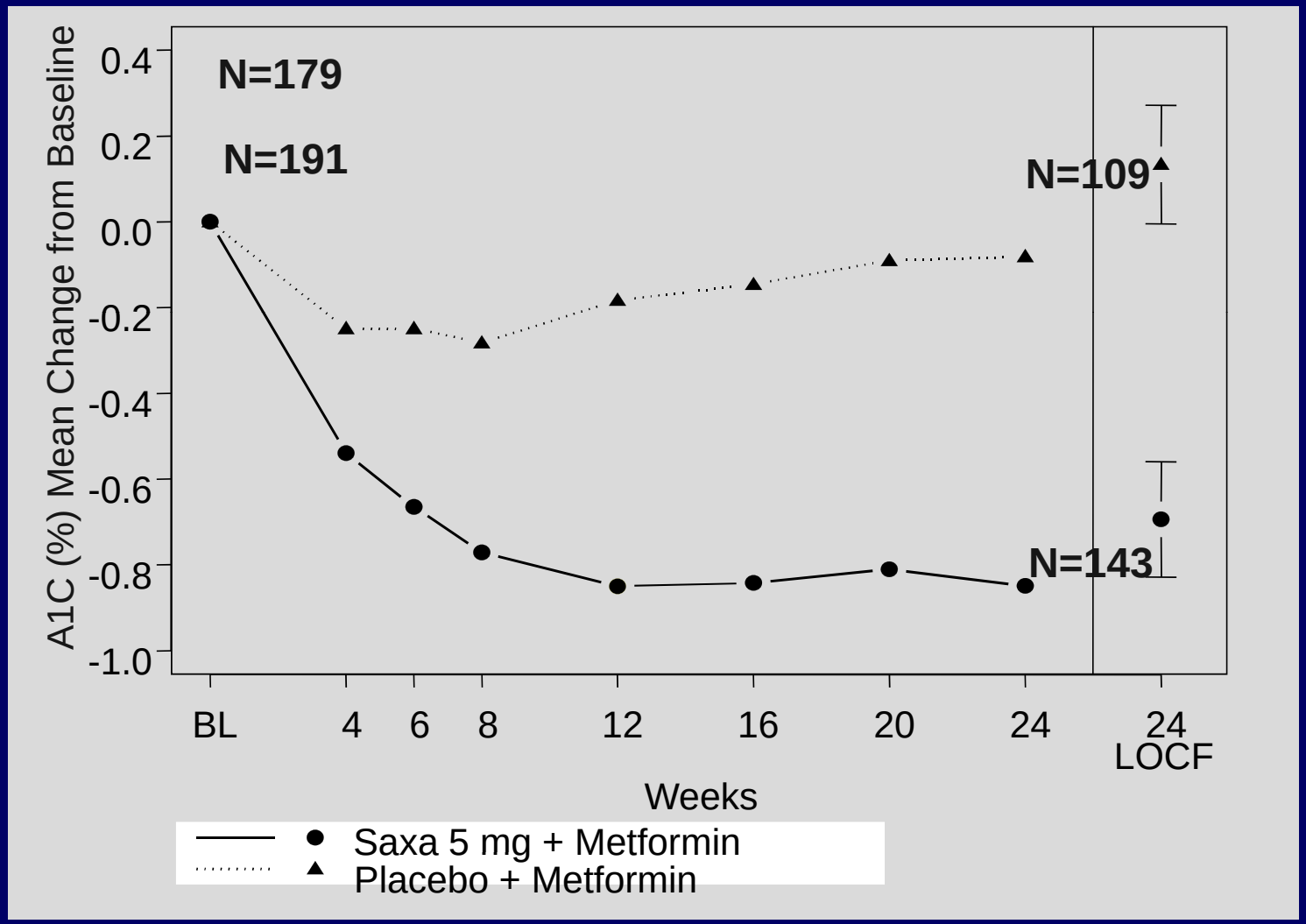
Brief Summary of Results
Pivotal Phase 3 Studies

- **Consistent, clinically meaningful and statistically significant reductions in HbA1c, Fasting Plasma Glucose, and Postprandial Plasma Glucose, as well as achievement of targets for HbA1c**
- **Range of adjusted mean differences for HbA1c, saxagliptin 5 mg vs placebo: 0.40% – 0.83% (saxagliptin 2.5 mg range: 0.36% - 0.73%)**
- **Discussion will focus primarily on HbA1c, saxagliptin 5 mg for simplicity**

Brief Summary of Results
Pivotal Phase 3 Studies – ST Disposition

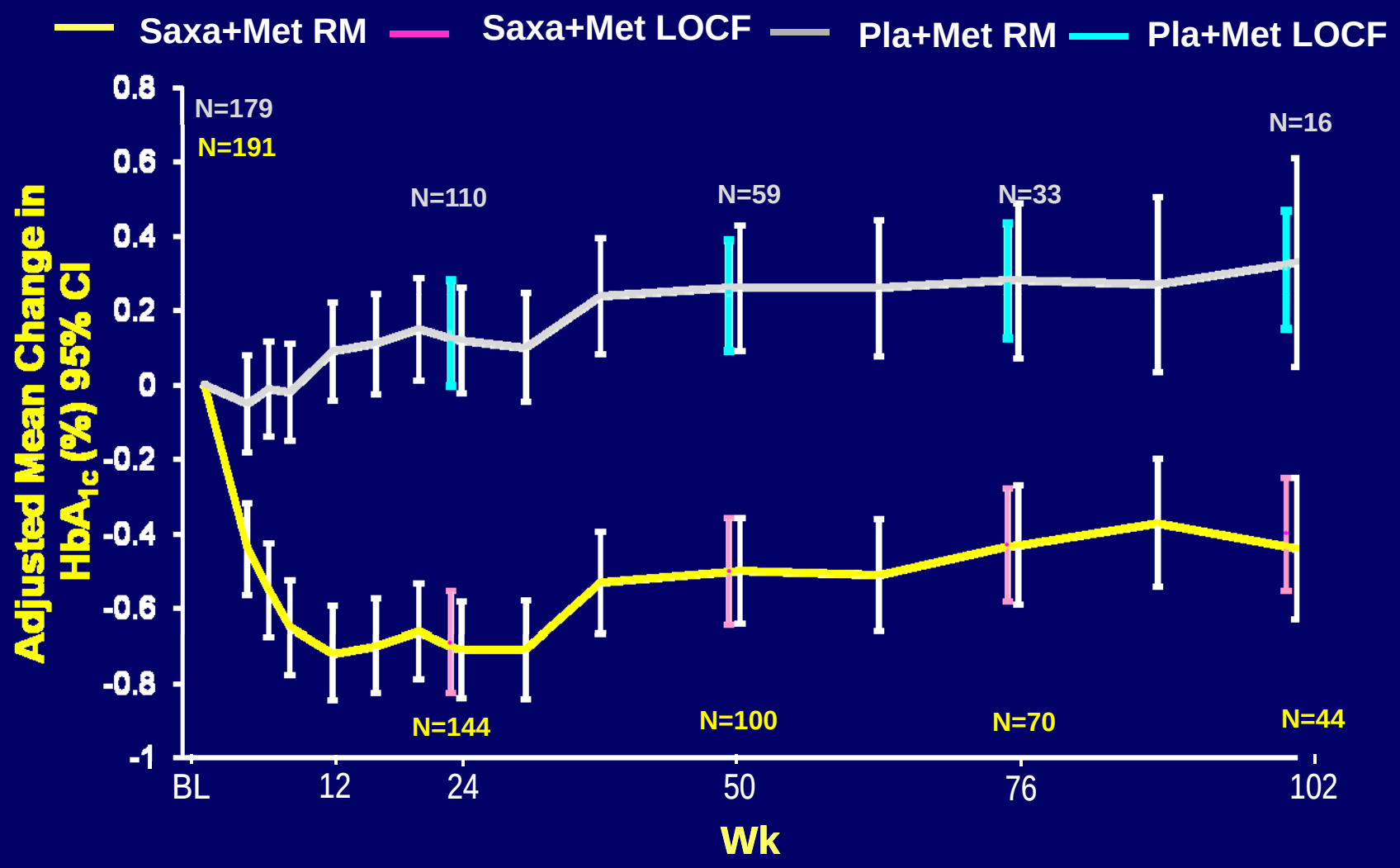


Mean Changes From Baseline HbA_{1c} Observed Over Time & Week 24 LOCF, Add-on to Metformin Study



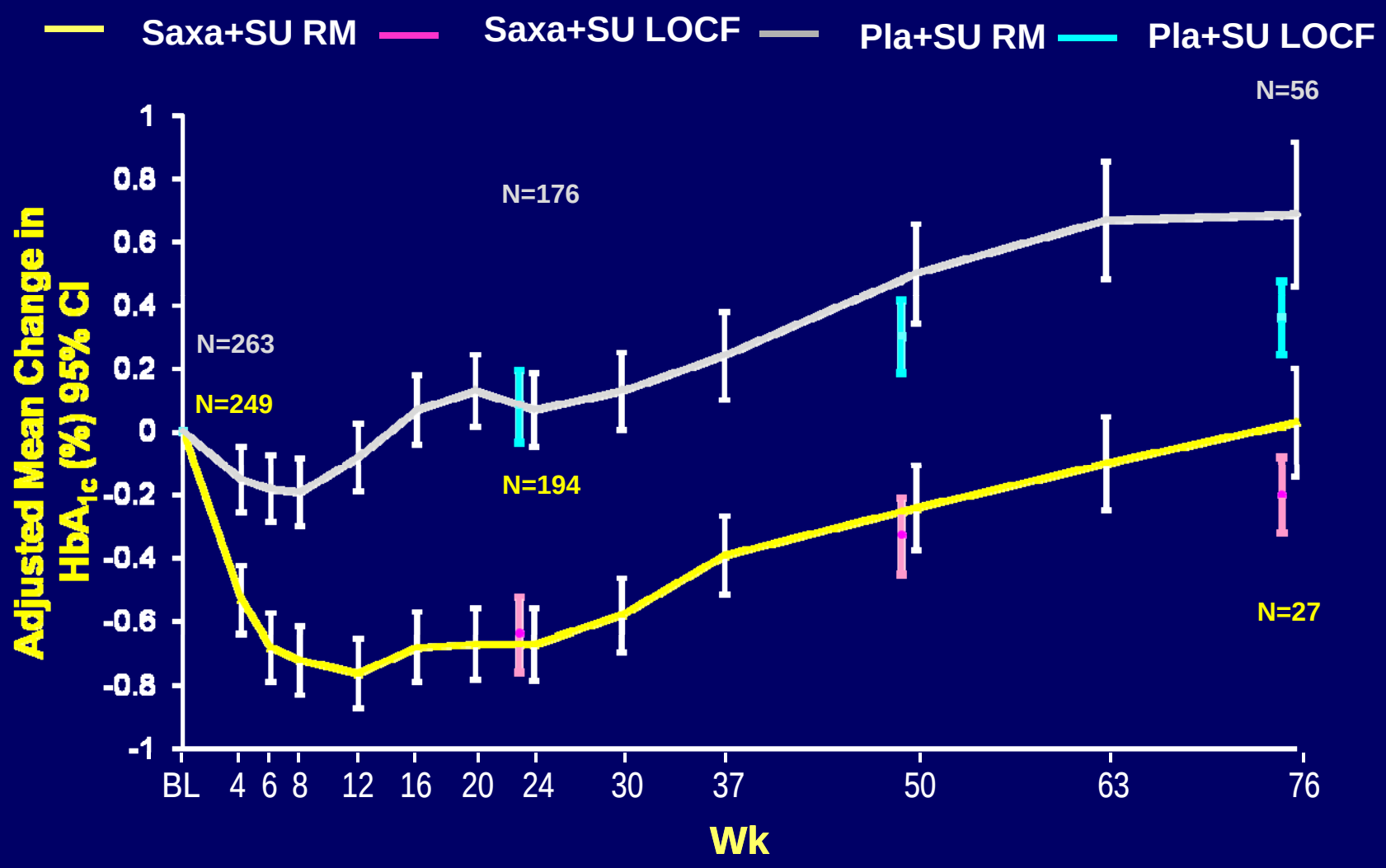
BL=baseline; HbA_{1c}=glycated hemoglobin; SAXA=saxagliptin.
N= represents counts of subjects with observed data from short-term database

Adjusted Mean Changes From Baseline HbA_{1c} Over 102 Wks, Add-on to Metformin Study



BL=baseline; HbA_{1c}=glycated hemoglobin; Met=Metformin; SAXA=saxagliptin PLA=placebo
RM= Repeated Measures LOCF=Last Observation Carried Forward.
N= represents counts of subjects with observed data from short-term + long-term database

Adjusted Mean Changes From Baseline HbA_{1c} Over 76 Wks, Add-on to SU Study



BL=baseline; HbA_{1c}=glycated hemoglobin; SU=Sulfonyurea; SAXA=saxagliptin PLA=placebo
RM= Repeated Measures LOCF=Last Observation Carried Forward.

Alternate Endpoints ?

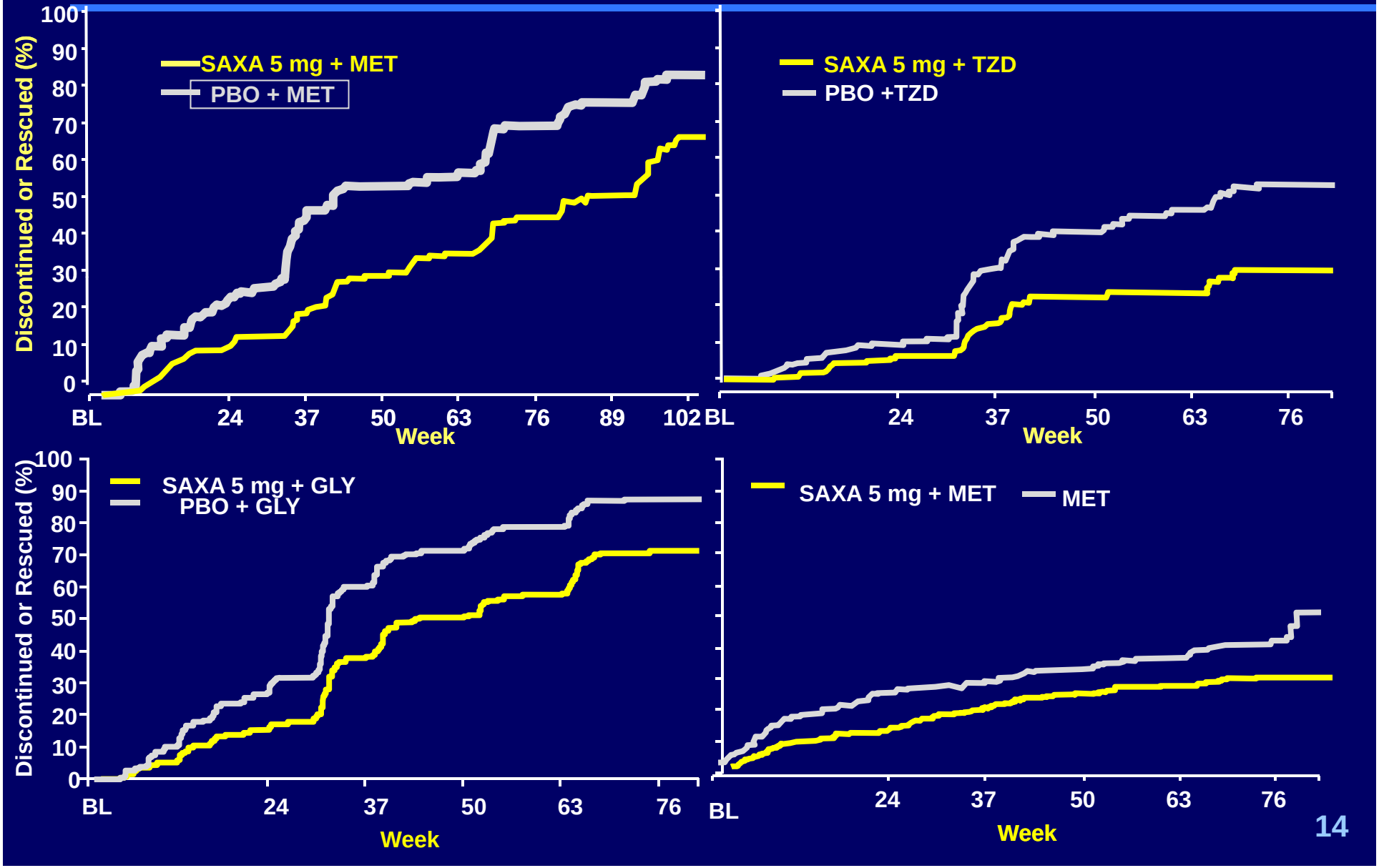
Discontinuation for lack of efficacy/rescue

- **EU diabetes guidance: A reduction in the proportion of patients who are withdrawn due to lack of efficacy compared to placebo according to study protocols may be used to provide additional support for efficacy.**
- **For example, time to treatment failure could include the use of alternative therapy as an indicator of treatment failure.**
- **But…discontinuation for other reasons still creates missing (censored) data. Also may be affected by choice of rescue criteria.**

Demonstrated treatment success

- **HbA1c < 7%, unrescued, observed value (treatment success). All other outcomes (discontinued, rescued) defined as treatment failure.**

Subjects Rescued or Discontinued Due to Lack of Efficacy



Results Incorporating Rescue

Prespecified models

- ANCOVA LOCF, repeated measures (up to rescue)

Varying sensitivity models

- ANCOVA LOCF, regardless of rescue
- Repeated measures, incorporating time-dependent covariate
- Repeated measures, regardless of rescue

General points

- HbA1c treatment effects from models for 24-week data generally differed by < 0.1%
- Rescue effects varied
- Regardless of rescue tended to smaller treatment effects
- No clear method “most conservative” in all cases

Experience with Other Missing Data Approaches

BOCF

- Additional single imputation technique (mentioned in EU missing data guidance)
- Assumes that subjects who discontinue return to baseline (not deriving benefit)
- Tends to be conservative, excluding placebo effect

MI

- Incorporates variability, widely acknowledged
- Used to demonstrate robustness, “Break the analysis approach”
- NMAR setting: assume that subjects in control arm like nonmissing (hot deck), but subjects in experimental arm increase to varying levels
- Incorporate subject-specific effects

Pattern Mixture / Selection Models

What is the Question?

Question of treatment effect at the primary timepoint is complicated by missing data. Can frame in a number of different ways, e.g.

Mean change in subjects who remain and do well on therapy

- Lose the randomization
- Different types of subjects in arms

Mean change at end of treatment

- End of treatment = time point of interest?
- Early termination value can substitute?

Mean change if subjects could not add additional medication (but could stop treatment)

- Assumes subjects lose benefits?

What is the Question?

Mean change in all subjects regardless of treatment termination or additional treatment

- **Treatment Strategy?**
- **Limiting case – changing the comparison?**
- **Insulin rescue**

Mean change if all subjects remained on treatment without additional medication

- **Hypothetical/contrafactual**
- **Assumptions unverifiable**

Mean change, taking out effects of any other medications added

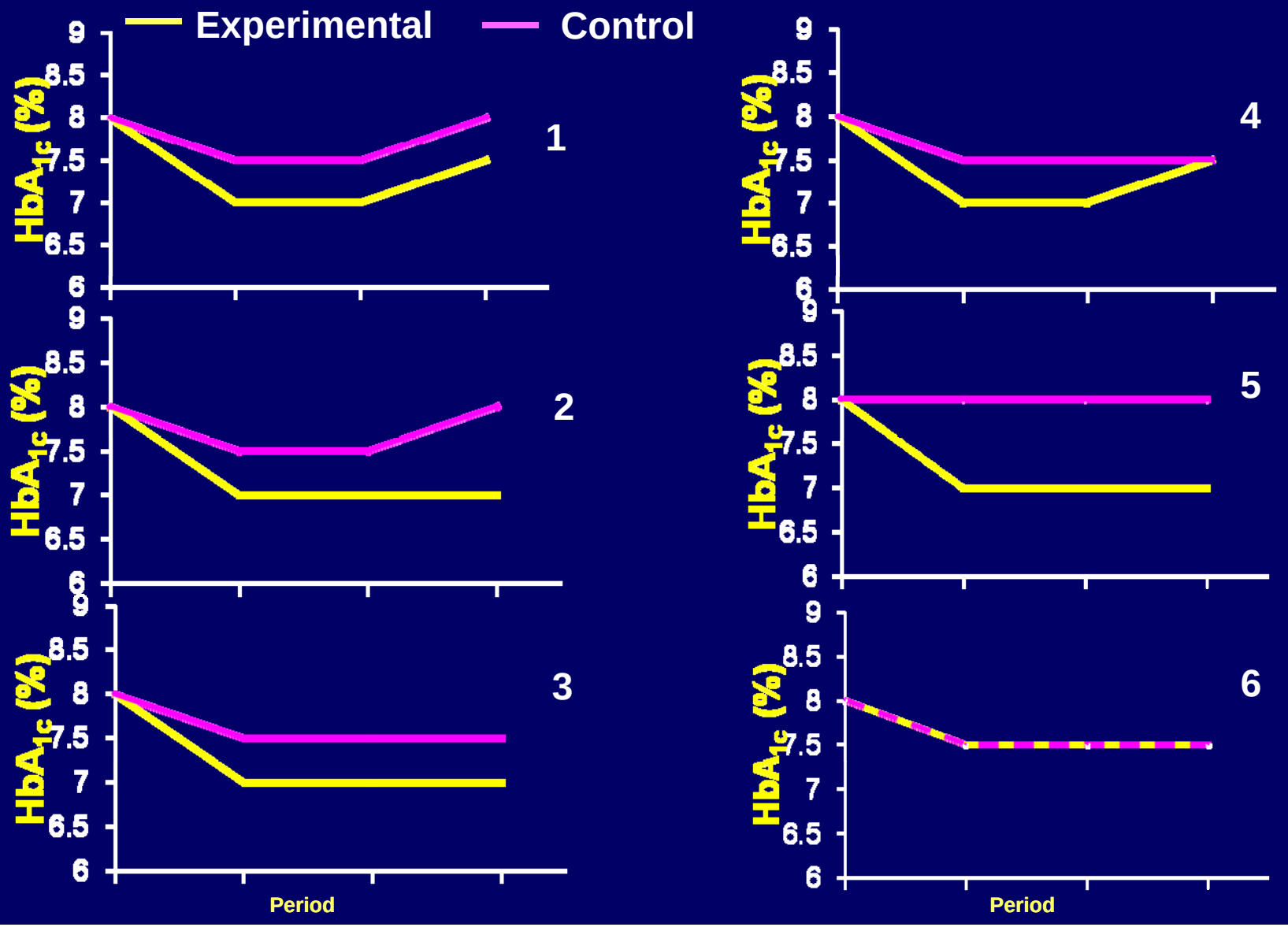
- **Nonrandomized medication?**

Simulation Study

Simulation study to assess behavior of current approaches

- **Hypothetical 4 period study, superiority hypothesis**
- **Analyses incorporating missing data approaches**
  - **Analyses using hypothetical data**
  - **LOCF, ANCOVA (prior to rescue, including rescue)**
  - **Completers, ANCOVA**
  - **Repeated measures analyses (prior to rescue, including rescue, modeling rescue)**
- **Measurement SD: 0.75%, correlation 0.5% between each timepoint**
- **6 scenarios**
- **5000 repetitions**
- **Random rescue effect {N(-0.5%, 0.5%)}**

Simulation Study - Scenarios



Simulation Results

Percent Missing by Treatment Group

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Experimental	15.4	15.4	15.4	15.4	15.4	38.4
Control	38.2	38.2	38.2	38.3	66.6	38.2

Mean Estimated Rescue Effect

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
	-0.51	-0.51	-0.51	-0.51	-0.52	-0.51

Simulation Results

Estimated Effect

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Simulated (hypothetical)	-0.50	-1.00	-0.50	-0.00	-1.00	0.00
ANCOVA LOCF	-0.47	-0.90	**-0.59**	**-0.16**	**-1.12**	0.00
ANCOVA OBS	-0.42	-0.92	-0.42	0.08	-0.81	-0.00
ANCOVA ITT	-0.38	-0.89	-0.39	0.11	-0.74	0.00
RMM	-0.50	-1.00	-0.50	0.00	-1.00	-0.00
RMM ITT	-0.38	-0.89	-0.39	0.11	-0.74	0.00
RMM TDC	-0.50	-1.00	-0.50	0.00	-1.01	0.00

Positive: control better; Negative: experimental better

Simulation Results

Percent P < 0.05

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Simulated (hypothetical)	99.9+	99.9+	99.9+	5.1	99.9+	5.1
ANCOVA LOCF	99.9+	99.9+	99.9+	**40.8**	99.9+	4.8
ANCOVA OBS	97.0	99.9+	97.2	11.9 (0.3)	99.9+	5.0
ANCOVA ITT	97.2	99.9+	97.2	22.0 (0.1)	99.9+	5.4
RMM	99.6	99.9+	99.6	5.6 (2.5)	99.9+	5.0
RMM ITT	97.6	99.9+	97.6	23.3 (0.0)	99.9+	6.3
RMM TDC	99.9	99.9+	99.9	6.1 (2.9)	99.9+	6.6

2-sided results. Numbers in parentheses indicate proportion in tail where experimental is significantly better

Additional Simulations

Modify correlation across timepoints

- **Generally similar to constant correlation**
- **Repeated Measures models tended to be closer to nominal type I error for negative case**

Mixture scenarios ("good" patients / "bad" patients)

- **ITT models lose power**
- **Observed ANCOVA also loses power**

Non-ignorable scenarios

- **LOCF ANCOVA anticonservative, TDC somewhat so, ITT conservative**
- **RMMM performed well**

Additional Simulations

Differential rescue effect

- Larger control rescue effect -> RMMs (ITT, TDC) conservative
- Larger experimental rescue effect -> RMMs (ITT, TDC) anticonservative
- ANCOVA models anticonservative

Considerations involving noninferiority

Discussion and Conclusions

Robustness of results/limitations: Clinical Data

- **Change from baseline affected by analysis, treatment differences generally consistent**
- **Proportion of missing data**

Behavior of different approaches: Simulations

- **ANCOVA models: conservative in many cases, but anticonservative in others**
  - **LOCF**
- **Repeated Measures:**
  - **Improvement on ANCOVA?**
  - **Performs well in MAR, some non-ignorable settings**
  - **Specification of correlations matter**
- **"ITT Approaches": generally conservative, sometimes very**

Discussion and Conclusions

Prevention of missing data

- **Greater awareness of implications of missing data to team**
- **Rescue criteria**
- **Role of post-rescue data in analysis**
- **Study periods (following rescue, complete ST before entering LT)**
- **Collect data off treatment**

Sample size

- **Considerations of missingness, analysis methods**

Discussion and Conclusions

Treatment of missing data

- **Question of interest**
- **Role of pre-specified sensitivity analyses (including post-rescue data)**
  - **Repeated measures v ANCOVA (LOCF)**
  - **ITT**
  - **Model rescue**
- **Additional approaches (endpoints)**

Sample References

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