Handling of Missing Data: Learnings from Saxenda® NDA

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- Background
- Steps taken to address the missing data problem
- Results
- FDA evaluation
- Summary and conclusion

Background

- Saxenda® (Liraglutide 3.0 mg) intended for weight management
- New drug application (NDA) submitted to FDA December 2013
- Advisory committee meeting (AdCoM) held on September 11th 2014
- Approved December 2014

- Phase 3 program
  - 3 placebo controlled trials of 56 week duration (body weight)
    - First trial initiated ~5 years prior to NDA
  - 1 placebo controlled trial of 32 week duration (sleep apnoea)

Weight management guideline:

- Full analysis set (FAS) should be all randomised with a post baseline observation
- Primary analysis should be based on last observation carried forward (LOCF)
- A product can be considered effective if after 1 year of treatment

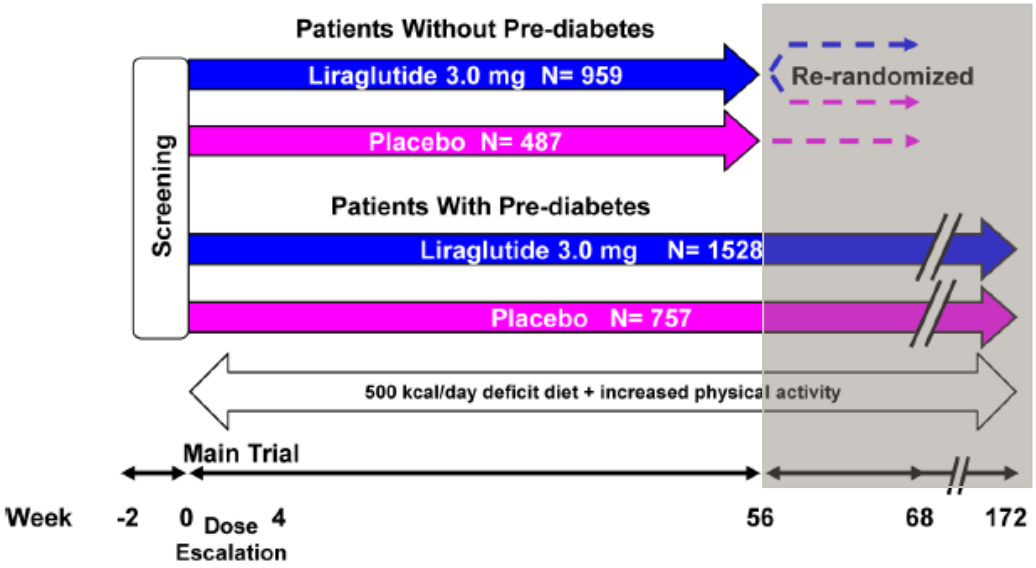
either

- difference in mean weight loss between active and placebo is at least 5 % and statistically significant

or

- proportion of subjects losing at least 5 % weight in active group is at least 35 %, is appr. double the proportion in placebo, and the difference between groups is statistically significant

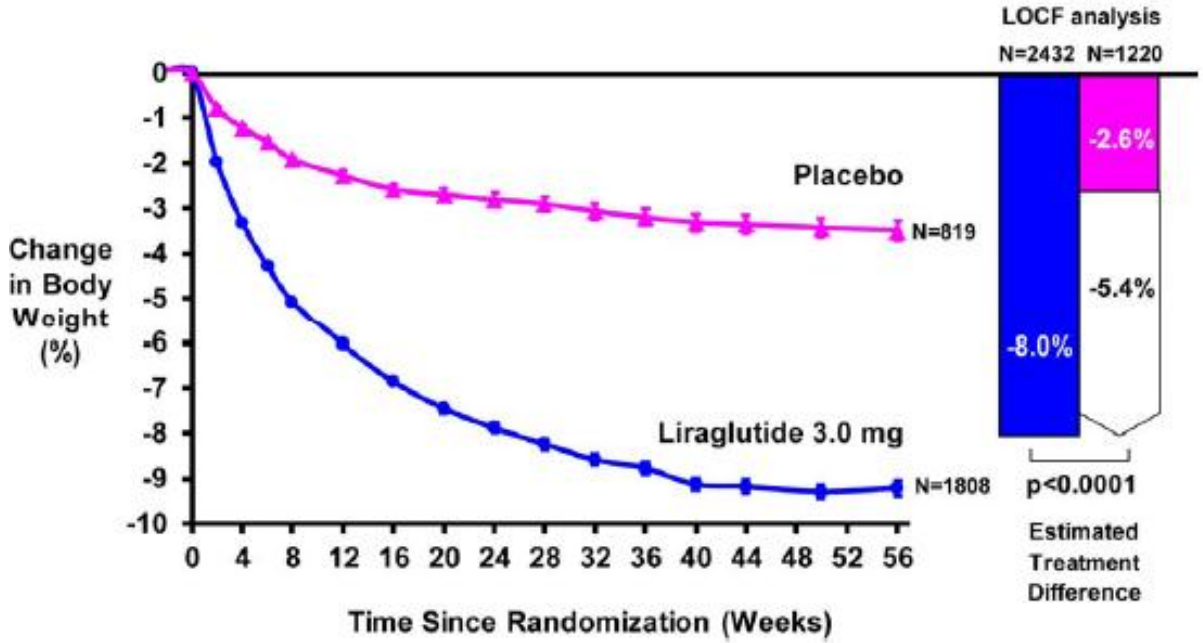
Trial Design – Largest phase 3 trial



Randomization 2:1. Stratification by pre-diabetes status at screening (2010 criteria[95]) and by BMI (≥30 kg/m^2 or <30 kg/m^2). Between 0 and 4 weeks liraglutide dose was escalated by 0.6 mg/week increments up to 3.0 mg.

- Parallel group, placebo controlled, double-blind
- Co-primary endpoints:
  - percent change in body weight at week 56
  - Proportion losing at least 5% at w56
  - Proportion losing more than 10% at w56
- Tested hierarchically to preserve the family-wise type I error at 5%

Body weight change from baseline (%) – Trial 1839



Data are observed means with standard error bars for patients completing each visit (numbers [N] completing are shown at the end of the curves). The estimated mean weight loss and treatment difference for patients included in the analysis

Addressing missing data

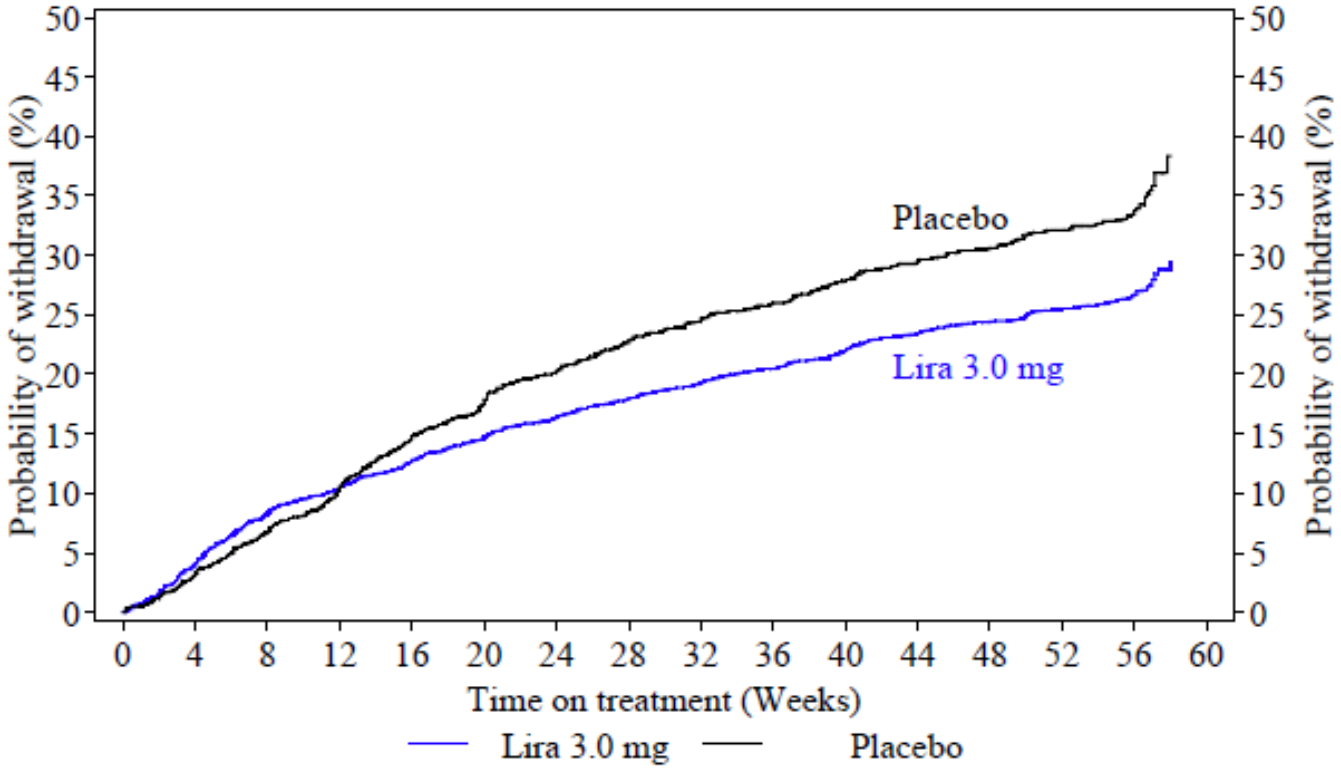
- Withdrawn patients invited for nominal week 56 (end-of-trial) visit to assess bodyweight (primary endpoint) and collect AE information
- Several sensitivity analyses using different imputation techniques carried out
  - Most pre-specified at protocol level
  - Some additional for the NDA
- Description of missing data patterns through plots
  - Withdrawal patterns and differences between arms have an impact on how the various missing data imputations works

Missing data

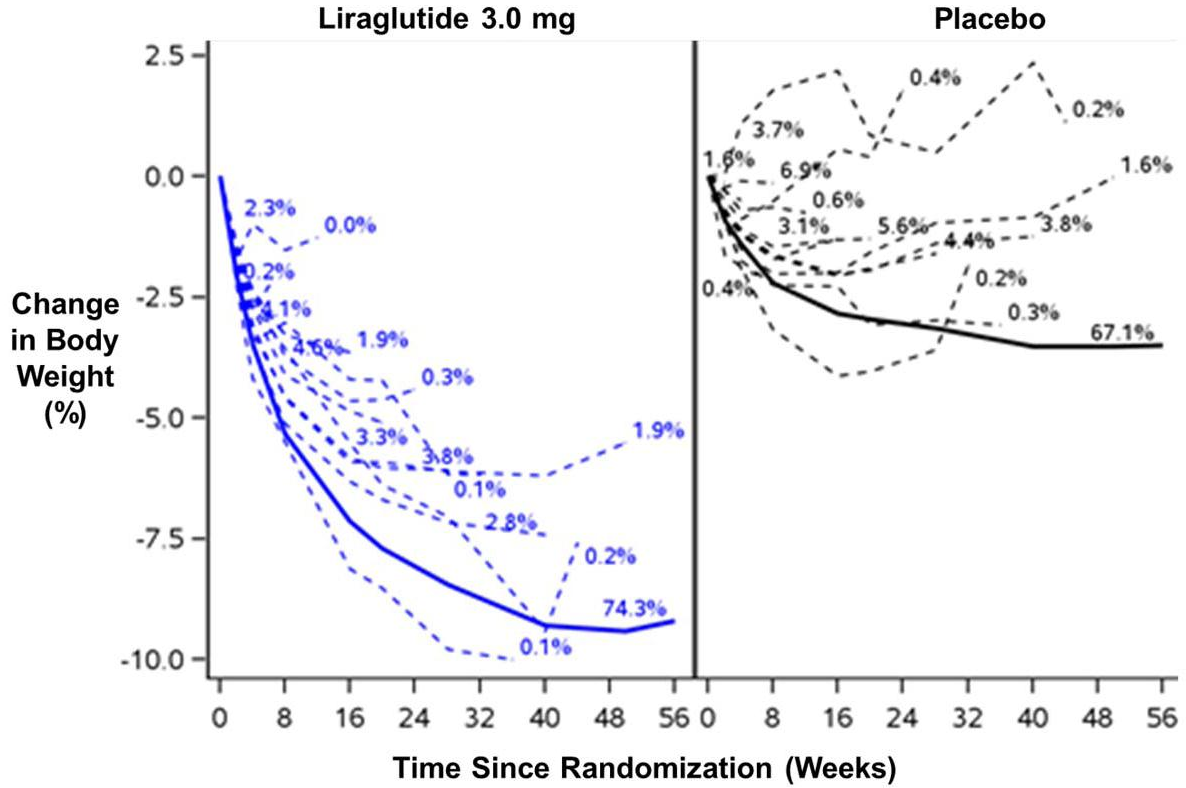
	Withdrawn		Withdrawn due to Adverse events		Withdrawn due to ineffective therapy	
Trial	Liraglutide 3.0 mg	Placebo	Liraglutide 3.0 mg	Placebo	Liraglutide 3.0 mg	Placebo
1839	28.1%	35.6%	9.6%	3.6%	0.9%	2.9%
1923	25.0%	30.5%	8.5%	8.6%	0.0%	1.1%
1922	23.4%	34.0%	9.2%	3.3%	0.0%	1.4%
3970	25.6%	20.7%	11.1%	3.4%	1.1%	0.6%

Missing data patterns

Time to discontinuation



Body weight change by last available on-drug measurement



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Proportion of withdrawn patients returning for week 56 visit – Retrieved drop-outs (RD)

Trial	Liraglutide 3.0 mg	Placebo
1839	28.2%	24.5%
1923	37.5%	40.0%
1922	38.6%	32.4%
3970	NA	NA

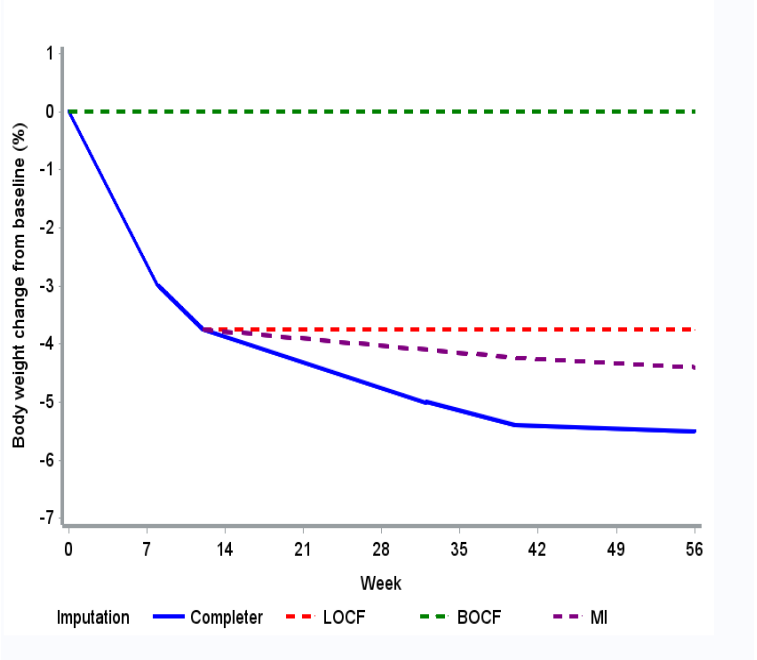
Imputation considerations

- Reasons for the missing data
  - Missing completely at random (MCAR)
  - Missing at random (MAR)
  - Missing not at random (MNAR)
- Imputations should preferably take the uncertainty of the imputed value into account
  - multiple imputation versus single imputation
- What is the scientific question of interest – the "estimand". E.g,:
  - ideal treatment effect that could have been reached if all patients had fully adhered (de-jure)
  - treatment effects that occur when full adherence to treatment is lacking (de-facto)
  - The estimand concept was not used in the NDA

"Well, this certainly explains much of the company's missing data. Who else thought the 'DEL' key on their computer was for delegating work?"

Analyses of % change in body weight

1. LOCF (primary)
2. "Retrieve drop-out": Using follow-up BW if available (30%) -rest imputed by LOCF
3. MMRM (cont. endpoint)
4. MI with sequential CR-type imputation
5. Completers only
6. LOCF plus BOCF for patients without post-baseline assessment
7. BOCF for all withdrawals not increasing weight during trial otherwise the observed weight increase was used as imputed value



1-5 : FAS defined as all patients with post baseline measurements,
6-7: All randomised
LOCF: last observation carried forward, BOCF: baseline observation carried forward, BW: Body weight
MMRM: mixed model repeated measurements, MI: Multiple imputation, CR: Copy reference

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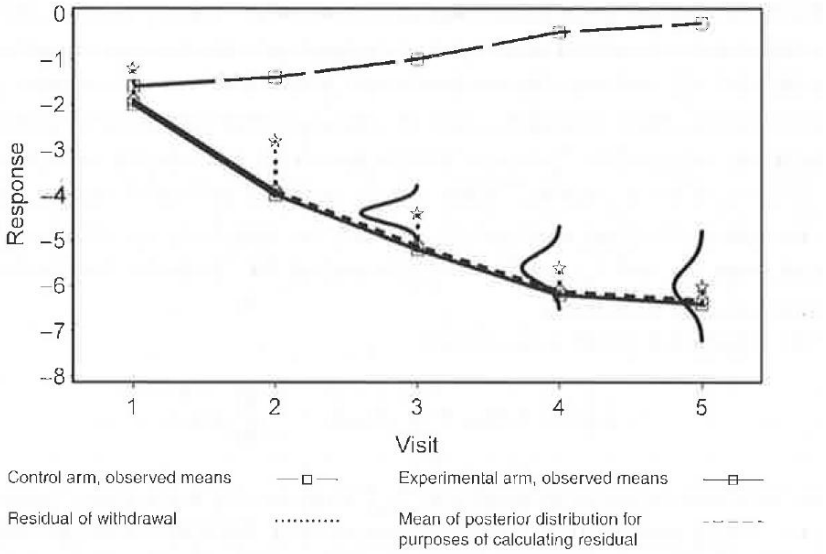
Repeated measures - MMRM

- Utilises all post baseline observations in the estimation of treatment difference at end-of-trial
- Assumes data are MAR - response trajectories for patients withdrawing from treatment are comparable to those for similar patients that complete treatment
- Estimate what would have been the result at the end of the trial had all patients remained in the trial and on treatment (a de-jure estimand addressing efficacy)

Missing at random (MAR)

- Example: Likely imputations for a patient in the Liraglutide 3.0 mg arm who withdraws after visit 2.



Source: Clinical trials with missing data: a guide for practitioners (2014), M. O'Kelly and B. Ratitch

Multiple Imputation - sequential copy reference - type imputation

1. Intermittent missing values imputed using a MCMC method to obtain a monotone missing data pattern. 100 copies of dataset generated

2. For each copy, ANOVA model with the same factors and covariates as the primary model was fitted to the second post-baseline visit value *for the completing placebo patients*. Estimated parameters, and their variances, from this model were used to impute missing values at the second post-baseline visit for WD patients in both treatment groups.

3. Missing values at the next planned visit imputed in the same manner, but also included the body weight value from the previous visit as a covariate in the model.
   - Repeated stepwise for all available planned visits.

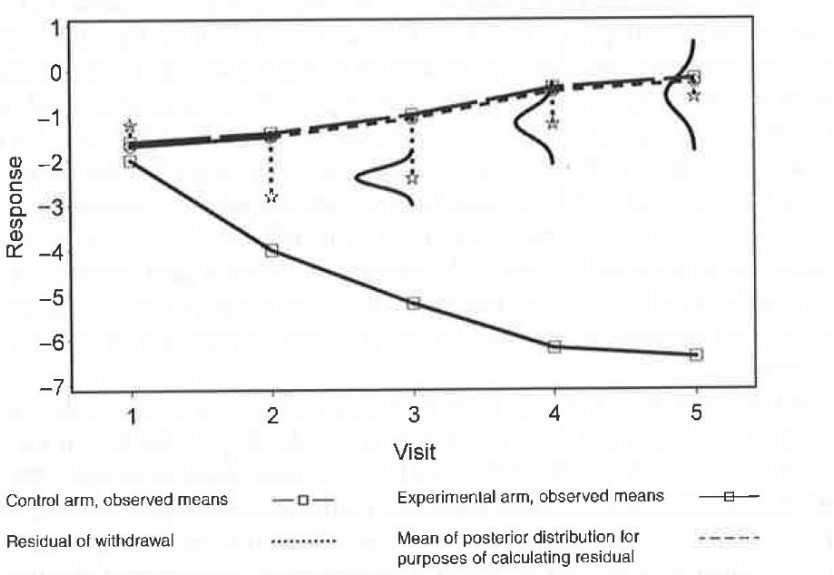
4. Estimates and SDs for the 100 data sets were pooled to one estimate and associated SD using Rubin’s rule

Multiple Imputation - sequential CR-type imputation

- Estimate what would have been the result at the end of the trial had all patients remained in trial and on diet an exercise after treatment discontinuation

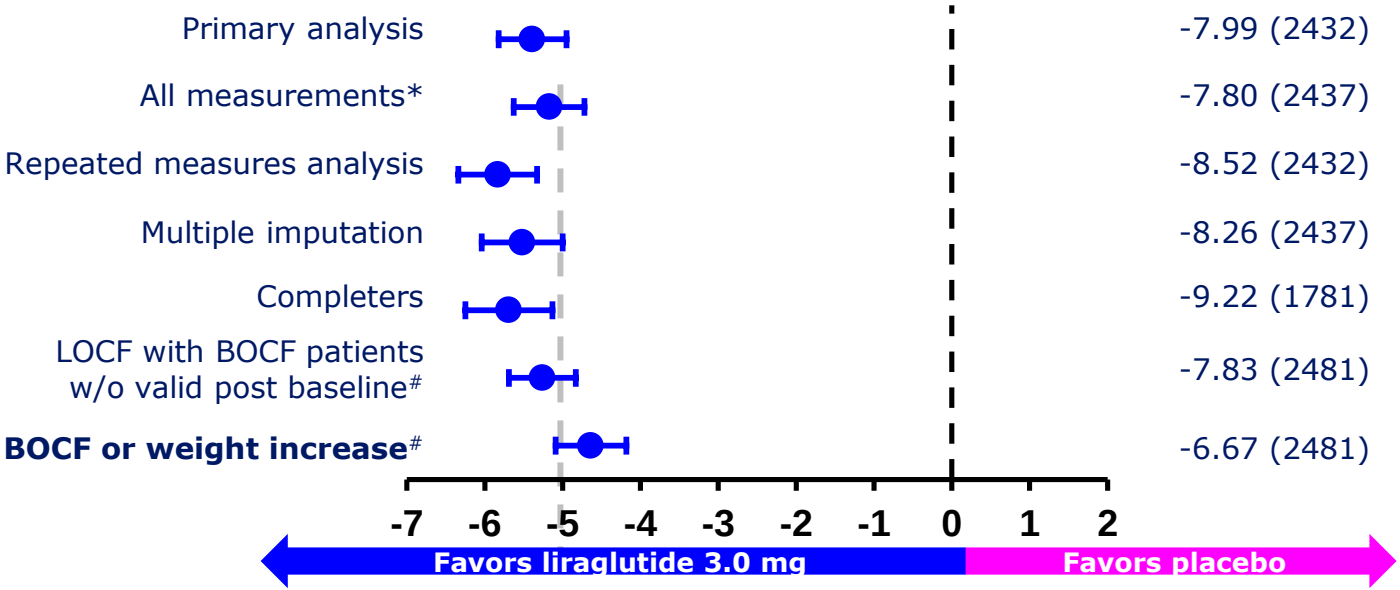
Copy reference

- ITT-like approach. The treatment effect gradually disappear after it has been discontinued.
- The patient's missing values when imputed will look like a rather successful patient in the reference group



Source: Clinical trials with missing data: a guide for practitioners (2014), M. O'Kelly and B. Ratitch

Sensitivity Analyses of Change in Body Weight (%) – Trial 1839



	Change from baseline (%)	
	Liraglutide 3.0 mg LSMean (N)	Placebo LSMean (N)
Primary analysis	-7.99 (2432)	-2.60 (1220)
All measurements*	-7.80 (2437)	-2.63 (1225)
Repeated measures analysis	-8.52 (2432)	-2.69 (1220)
Multiple imputation	-8.26 (2437)	-2.74 (1225)
Completers	-9.22 (1781)	-3.53 (798)
LOCF with BOCF patients w/o valid post baseline#	-7.83 (2481)	-2.57 (1239)
BOCF or weight increase#	-6.67 (2481)	-2.04 (1239)

NDA; FAS at end-of-treatment. #All randomized. N, number of patients contributing to analysis. *All measurements included fasting and non-fasting weight measurements, off drug measurements, and follow-up measurements after 56 weeks of randomization for patients who discontinued.

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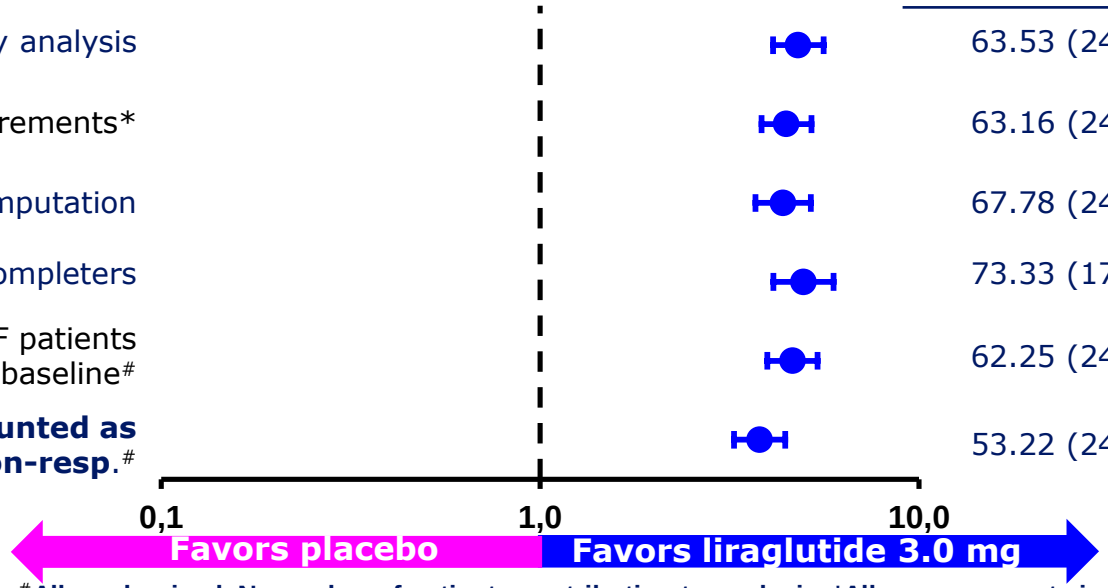
Sensitivity Analysis for Achieving ≥5% Weight Loss – Trial 1839



	5% responders at end of trial (%)	
	Liraglutide 3.0 mg LSMean (N)	Placebo LSMean (N)
Primary analysis	63.53 (2432)	26.61 (1220)
All measurements*	63.16 (2437)	27.74 (1225)
Multiple imputation	67.78 (2437)	32.46 (1225)
Completers	73.33 (1781)	35.68 (798)
LOCF with BOCF patients w/o valid post baseline[#]	62.25 (2481)	26.22 (1239)
Early withdrawals counted as non-resp.[#]	53.22 (2481)	23.05 (1239)

NDA; FAS at end-of-treatment. [#]All randomized. N, number of patients contributing to analysis. *All measurements included fasting and non-fasting weight measurements, off drug measurements, and follow-up measurements after 56 weeks of randomization for patients who discontinued.

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Feedback - FDA

- LOCF not acceptable
- FDA considered FAS as being *all randomised*
- NN sensitivity analyses inadequate as they generally reflects a *de-jure* analysis rather than a *de-facto* analysis
  - Multiple Imputation method applied to Per-Protocol like
  - Imputed values do not agree with observed values for retrieved drop-outs in Liraglutide 3.0 mg arm
- FDA notes that for retrieved drop-outs, placebo patients on average loose weight from WD visit to FU visit, whereas the opposite is the case for Liraglutide 3.0 mg patients

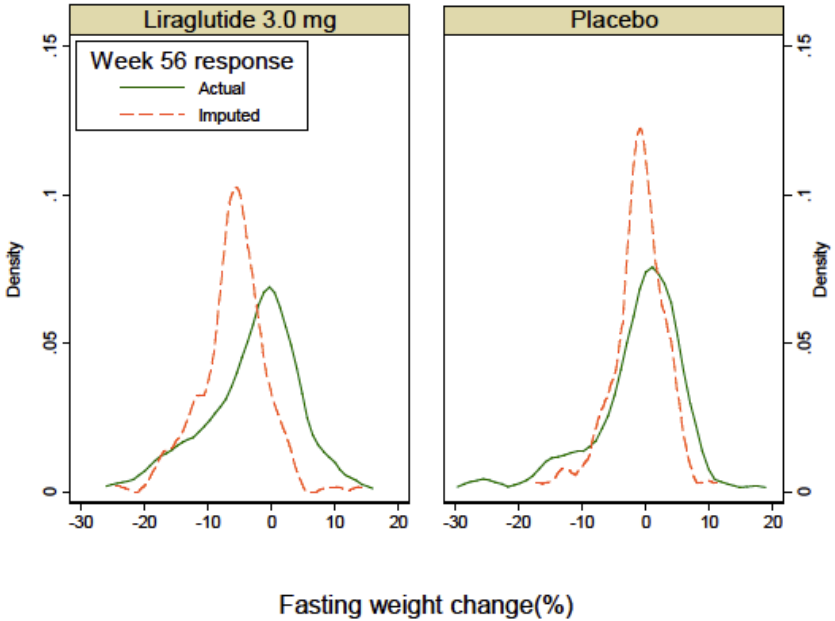
Comparison of weight change at last visit before withdrawal and at week 56 for RD patients

Treatment Group	N	LAO-OT Mean (SE)	Week 56 (Actual) Mean (SE)	Mean Difference; LAO-OT – Week 56 (95% CI)
Trial 1839				
Liraglutide 3.0 mg	171	-4.9% (0.4)	-3.0% (0.6)	-1.8% (-2.7, -1.0)
Placebo	100	-0.4% (0.4)	-1.3% (0.7)	0.9% (-0.4, 2.1)
Trial 1922				
Liraglutide 3.0 mg	33	-4.4% (0.7)	-2.5% (0.8)	-1.8% (-3.2, -0.5)
Liraglutide 1.8 mg	8	-4.3% (1.3)	-2.4% (1.8)	-1.9% (-5.1, 1.3)
Placebo	23	-1.4% (0.4)	-1.7% (0.7)	0.3% (-1.5, 2.0)
Trial 1923				
Liraglutide 3.0 mg	12	-6.4% (1.0)	-1.1% (1.9)	-5.3% (-7.8, -2.8)
Placebo	18	-0.5% (1.0)	-1.1% (2.0)	0.5% (-2.8, 3.8)

Source: FDA statistical reviewer

LAO-OT: Last observation on treatment

Smoothed histograms of actual and imputed weight changes for RD patients using NN MI method



Source: FDA statistical reviewer

FDA comments to NN MI:

- Imputation for Liraglutide arm appear over-optimistic
- This will lead to biased results

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FDA sensitivity analyses

- FDA performed two sensitivity analyses of their own:
  - MI-RD (stated as their preferred approach):
    - Combined follow-up measurements from returning drop-outs with a MI approach:
      - MI based on observed follow-up measurements from returning drop-outs.
      - Grouping patients by treatment and time of last on-treatment measurement
    - Imputes under a MAR assumption

  - RD-Weighted:
    - Continuous endpoint analysed using weighted ANCOVA:
      - Completers assigned a weight of 1
      - Withdrawals not returning assigned a weight of zero
      - Returning drop-outs weighted depending on time of last on-treatment value
    - Imputes under a MCAR assumption

Most Conservative Sensitivity Analyses - NN versus FDA analyses – Trial 1839

	Difference Liraglutide to Placebo [95% CI]
Change in body weight (%)	
NN: BOCF or weight increase	-4.6 [-5.1; -4.2]
FDA: MI-RD	-4.8 [-5.3; -4.3]
FDA: RD-Weighted	-4.6 [-5.4, -3.9]

All randomized

Most Conservative Sensitivity Analyses - NN versus FDA analyses – Trial 1839

	LSMean Liraglutide 3.0 mg	LSMean Placebo
Achieving ≥5% weight loss		
NN: non-responders	**53%**	**23%**
FDA: MI-RD	**62%**	**34%**
FDA: RD-Weighted	**62%**	**31%**

All randomized

Difference between treatments were statistical significant for all

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Limitations of the FDA approach

- The RD patients may not be representative of the non-RD patients
  - Only ~30% of withdrawn patients were RD
  - RD placebo patients continued to lose weight after withdrawal

Summary and conclusion

- LOCF unacceptable
- No unique imputation method will address the missing data
- It is likely that additional post-hoc sensitivity analyses are needed
- Retrieval of follow-up information for withdrawn patients is considered important
  - FDA did not agree with NN definition of missing data
- The efficacy of Liraglutide 3.0 mg not questioned – only the magnitude of the effect