

Endocrinologic and Metabolic Drugs Advisory Committee Meeting Hyattsville, MD September 11, 2014

FDA Introductory Remarks

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Discussion Points

1. Please comment on whether the sponsor has provided adequate evidence to establish the efficacy of liraglutide 3 mg per day for chronic weight management. In your discussion, comment on the extent to which the observed effects on endpoints related to weight-related comorbidities factor into your assessment of the benefits of liraglutide for the proposed population.

Discussion Points

2. Discuss the safety profile of liraglutide for chronic weight management. In your discussion, please consider the following, including your level of concern for the contribution of liraglutide to these potential risks:
 - a. Neoplasms, including medullary thyroid carcinoma
 - b. Gallbladder-related events
 - c. Pancreatitis
 - d. Cardiovascular safety
 - e. Psychiatric events, including suicidality
 - f. Any other safety concerns

Discussion Points

3. Discuss the safety database for liraglutide 3 mg per day for chronic weight management, given the extent of clinical trial and post-marketing experience with liraglutide for diabetes mellitus with doses up to 1.8 mg per day.
 - a. How does the experience with liraglutide for diabetes mellitus inform the safety profile of liraglutide 3 mg per day for chronic weight management, given the different patient populations and doses?

Discussion Points

- b. Labeling for Victoza (liraglutide up to 1.8 mg per day), which is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, states that Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the thyroid C-cell tumor findings identified in rodents. If the current application were approved as proposed, it would be presumed that there would be no recommendation against using liraglutide 3 mg per day as initial therapy, for weight management, for patients with diabetes mellitus with BMI 27 kg/m² or greater. Discuss the implications of this overlap in populations and any concerns it may raise.

Discussion Points

- c. There is an ongoing cardiovascular outcomes trial to assess the CV risk of liraglutide in type 2 diabetes mellitus. The maximum dose of liraglutide in this trial is 1.8 mg per day. Discuss whether this trial would be sufficient to characterize the CV risk of liraglutide 3 mg per day for weight management.

Voting Question

4. Considering the currently available data and the proposed Risk Evaluation and Mitigation Strategy (REMS), is the overall benefit-risk assessment of liraglutide 3 mg per day favorable to support its approval for chronic weight management in individuals with a BMI 30 kg/m² or greater, or 27 kg/m² or greater in the presence of at least one weight-related comorbidity?
 - a. If voting YES, please provide your rationale and whether you recommend any additional studies post-approval.
 - b. If voting NO, please provide your rationale and discuss what additional data would be necessary prior to approval to address your concerns.

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Liraglutide for Chronic Weight Management
Clinical Efficacy and Safety Review

Julie Golden, M.D.
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Outline

- Background (Golden)
- Efficacy
 - Clinical considerations (Golden)
 - Statistical methods and perspective (McEvoy)
- Safety
 - Selected safety issues from clinical trials (Golden, Hampp)
 - Post-marketing safety (Hampp, Ryan, Zemskova)
- Summary and Benefit-Risk (Golden)



Background

Liraglutide

Diabetes and Weight Management

	Type 2 Diabetes	Weight Management
Dose	1.2 mg to 1.8 mg	3 mg
Indicated patient population	Adults with type 2 diabetes mellitus (T2DM)	Adult patients with an initial body mass index (BMI) of 30 kg/m ² or greater or 27 kg/m ² or greater in the presence of at least one weight related comorbidity
Limitation of Use: First-line therapy	Not recommended	None proposed

Regulatory History

Weight Management Drugs

- Draft FDA guidances 1996, 2007
 - Established 5% weight loss as clinically meaningful
 - Chronic therapy
- National Research Council Panel on Missing Data in Clinical Trials 2010
- Meridia (sibutramine) withdrawn from U.S. market 2010
- Cardiovascular Assessment of Obesity Drugs EMDAC meeting 2012
- Belviq (lorcaserin) approved 2012
- Qsymia (phentermine/topiramate XR) approved 2012

Liraglutide for Weight Management Dose Selection

Trial 1807

Phase 2 Dose-Response

- 20-week dose-ranging trial
 - Liraglutide 1.2 mg, 1.8 mg, 2.4 mg, 3 mg
 - Placebo
 - Open-label orlistat
- Extension (20-52 wk randomized, 52-104 wk open-label liraglutide)
 - Patients re-consented at week 20 (66-77% of randomized patients); limits efficacy conclusions
 - Generally supports continued dose-response

Liraglutide 3 mg Selected for Phase 3 Trial 1807, Weight Change at 20 Weeks

76% female, mean age 46 yrs, 98% white, mean BMI 35 kg/m², mean weight 96 kg

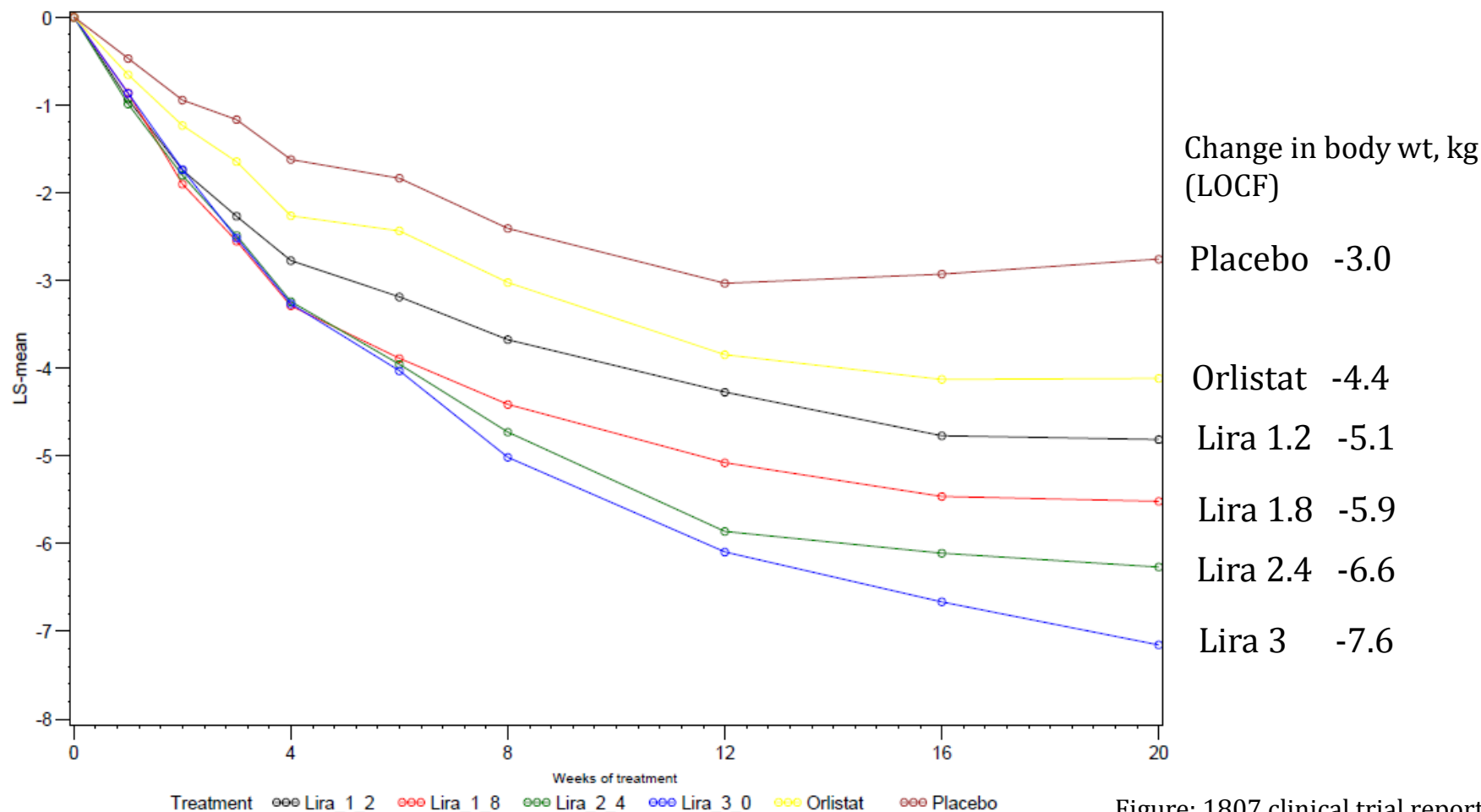


Figure: 1807 clinical trial report

Liraglutide 3 mg Selected for Phase 3 Trial 1807, Withdrawals and Adverse Events

	Placebo N=98	Lira 1.2 N=95	Lira 1.8 N=90	Lira 2.4 N=93	Lira 3 N=93	Orlistat N=95
Withdrawals	19%	11%	18%	22%	12%	17%
AEs	3%	4%	6%	10%	5%	3%
Ineffective	2%	1%	1%	0	0	1%
Adverse events	83%	85%	88%	90%	95%	85%
Gastrointestinal disorders	31%	54%	60%	67%	71%	55%

Weeks 0-20

Liraglutide for Weight Management Phase 3 Trials

Phase 3 56-Week Weight Loss Trials

	1923		1839		1922		
N (ITT)	Lira 3 212	Pbo 210	Lira 3 2487	Pbo 1244	Lira 3 423	Lira 1.8 211	Pbo 212
Patient Population	BMI ≥ 30 or ≥ 27 with dyslipidemia and/or HTN; achieved 5% wt loss during 4-12 wk run-in		BMI ≥ 30 or ≥ 27 with dyslipidemia and/or HTN; stratified by normoglycemia, pre-DM at screening		BMI ≥ 27 with T2DM HbA1c 7-10% Diet- or OAD-treated (max 30% SUs at baseline)		
Demographics	81%F / 46 y / 84%W		79%F / 45 y / 85%W		50%F / 55 y / 83%W		
Off-drug follow-up period	Yes 12 weeks		No		Yes 12 weeks		
Re-randomized period	No		Yes (normoglycemic pts) 12 weeks		No		
Extension period	No		Yes (pre-DM pts) 2 years		No		

F: female, W: white, HTN: hypertension, OAD: oral anti-diabetic medication, SU: sulfonylurea

56-Week Phase 3 Trials, General Comments

- 56-week duration intended to allow for a full 52 weeks at the 3 mg dose after 4-week titration period
- Each trial designed to answer a different question
 - 1923: weight loss/weight maintenance/prevention of weight regain after initial weight loss
 - 1839: stratified by pre-diabetes status, randomized withdrawal
 - 1922: patients with type 2 diabetes, 2 doses
- Limitations
 - Missing data: ~23% to 36% of patients discontinued during 56 weeks
 - 1923: self-selected group (diet responders)
 - 1922: more patients on placebo “rescued” for hyperglycemia

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Statistical Assessment of Efficacy

Bradley McEvoy, DrPH
Statistical Reviewer
DB II, OB, OTS, CDER, FDA

Outline

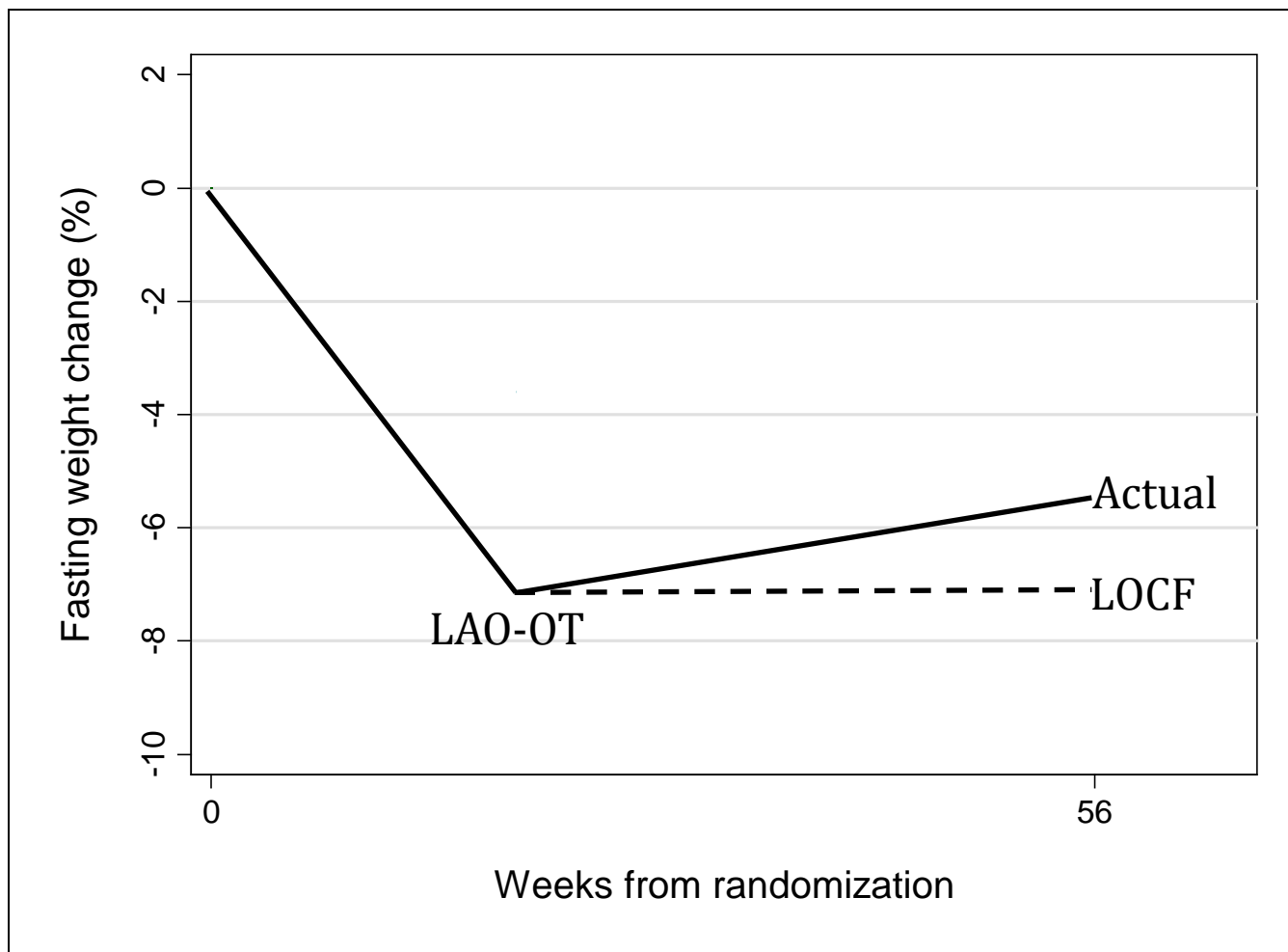
- Sponsor's primary analysis
- FDA analysis
- Results
- Conclusions

Trials 1839, 1922, 1923

- Primary endpoint: Change in fasting weight from baseline to week 56
 - Continuous: % change
 - Categorical: % reduction is at least 5%
- Sponsor's primary analysis imputed endpoint using last available observation on-treatment (LAO-OT)
 - Modified last observation carried forward (LOCF) imputation since off-treatment measurements were not used
- Subjects that discontinued were asked to come back for week 56 assessment. Ones that did are "retrieved dropouts"

National Academy of Science (NAS) Report

- View of missing data evolved following the 2010 NAS report on prevention and treatment of missing data
- Recommendation 10: Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified



Inadequacy of LAO-OT Week 56 Imputation for Retrieve Dropouts

Treatment Group	N	Imputed (LAO-OT) Mean change from baseline	Actual Mean change from baseline	Week 56 – LAO-OT
<i>Trial 1839</i>				
Lira 3.0 mg	171	-4.9%	-3.0%	1.8%
Placebo	100	-0.4%	-1.3%	-0.9%
<i>Trial 1922</i>				
Lira 3.0 mg	33	-4.4%	-2.5%	1.8%
Placebo	23	-1.4%	-1.7%	-0.3%
<i>Trial 1923</i>				
Lira 3.0 mg	12	-6.4%	-1.1%	5.3%
Placebo	18	-0.5%	-1.1%	-0.5%

Sponsor's Primary Analysis & Retrieved Dropouts – Comments

- Concern that the prespecified analysis exaggerates the treatment effect at week 56
 - Change for liraglutide over-stated
 - Change for placebo under-stated
- Subjects that discontinued but did not return for a follow-up assessment (non-retrieved dropouts)
 - Not likely represented by retrieved dropouts
 - Retrieved dropouts are arguably the best group to describe what happened to them at week 56

Characterizing the Treatment Effect

- Preferred approach – use the response from the landmark (week 56) visit, regardless of treatment adherence
- Intention-to-treat (ITT) analysis
 - What would the effect seen in practice if this treatment were applied to the population defined by the trial inclusion criteria (Kenward et al.)
- Fasting weight not measured at landmark visit for all subjects

Discontinuation and Missing Data

	Trial 1839		Trial 1922		Trial 1923	
	Lira 3.0 mg N=2487	Placebo N=1244	Lira 3.0 mg N=423	Placebo N=212	Lira 3.0 mg N=212	Placebo N=210
Discontinued	28%	36%	23%	34%	25%	30%
Retrieve dropout*	29%	25%	36%	32%	42%	39%
Fasting wt. (wk 56)						
Missing	20%	26%	16%	26%	17%	19%
Available	80%	74%	84%	74%	83%	81%
<i>On-treatment</i>	73%	66%	75%	55%	74%	69%
<i>Retrieve dropout</i>	7%	8%	9%	11%	10%	12%
<i>Other‡</i>	0.2%	0.4%	1%	8%	0%	1%

* Percent of subjects that discontinued

‡ Within landmark visit window but was neither retrieve dropout nor on-treatment

FDA Analysis

- Represent missing fasting weight at the landmark visit using information from retrieved dropouts
 1. Multiple imputation (MI; Trials 1839 & 1922)
 - Different from the sponsor's MI analysis
 2. Weighted Analysis (Trials 1839, 1922 & 1923)
- Analysis methods
 - Continuous: ANCOVA model
 - Categorical: Risk difference
- Analysis population: All randomized with a baseline assessment

FDA Analysis – Comments

- Preference is to have complete endpoint ascertainment
- Rely on untestable assumptions and use statistical modeling to predict what the response at the landmark visit would have been if it was measured

Results: Trial 1839

	Lira 3.0 mg Mean change	Placebo Mean change	Lira – Placebo (95% CI)
Fasting weight change (%)			
MI (ITT)	-7.4%	-2.8%	-4.6% (-5.4, -3.9)
Weighted (ITT)	-7.5%	-2.8%	-4.8% (-5.3, -4.3)
LOCF (FAS)	-8.0%	-2.6%	-5.4% (-5.8, -5.0)
	Lira 3.0 mg %	Placebo %	Lira - Placebo (95% CI)
Fasting weight reduction exceeds 5%			
MI (ITT)	62%	34%	28% (24, 32)
Weighted (ITT)	62%	31%	31% (28, 34)
LOCF (FAS)	63%	27%	36% (33, 39)

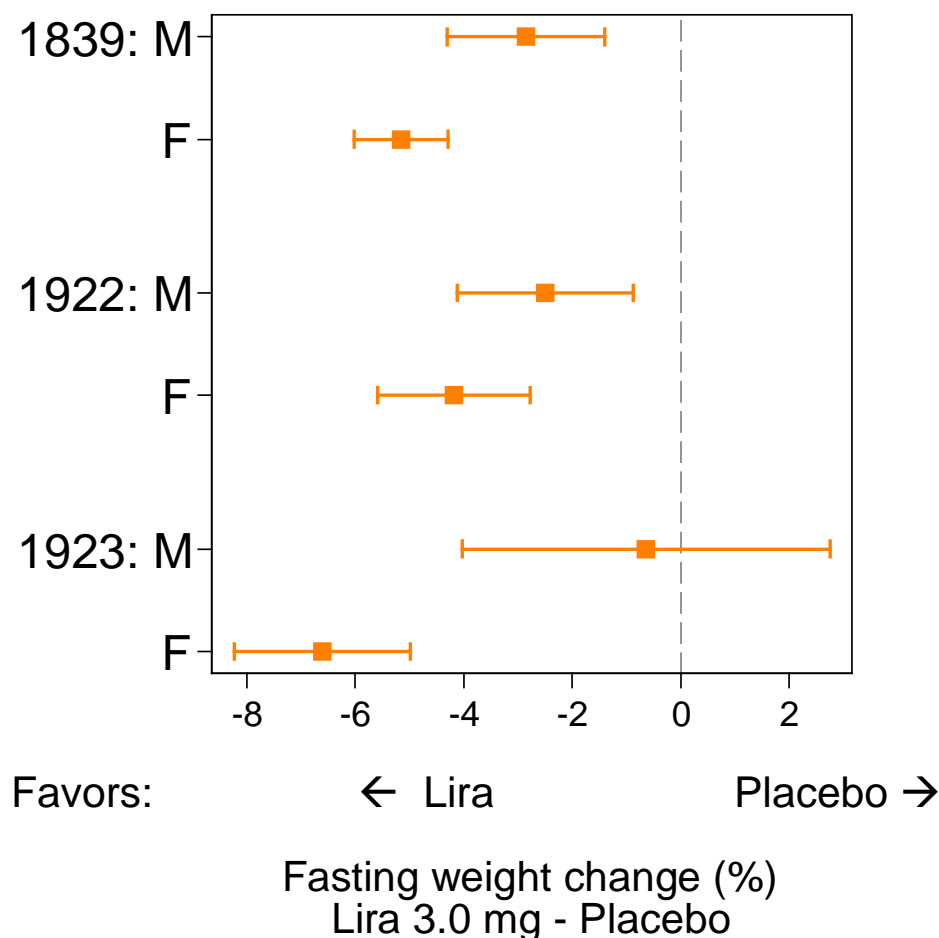
Results: Trial 1922

	Lira 3.0 mg Mean change	Placebo Mean change	Lira – Placebo (95% CI)
Fasting weight change (%)			
MI (ITT)	-5.7%	-2.2%	-3.4% (-4.5, -2.3)
Weighted (ITT)	-5.8%	-2.0%	-3.8% (-4.7, -2.9)
LOCF (FAS)	-5.9%	-2.0%	-4.0% (-4.8, -3.1)
	Lira 3.0 mg %	Placebo %	Lira - Placebo (95% CI)
Fasting weight reduction exceeds 5%			
MI (ITT)	50%	20%	31% (22, 39)
Weighted (ITT)	51%	15%	36% (29, 42)
LOCF (FAS)	50%	14%	36% (29, 43)

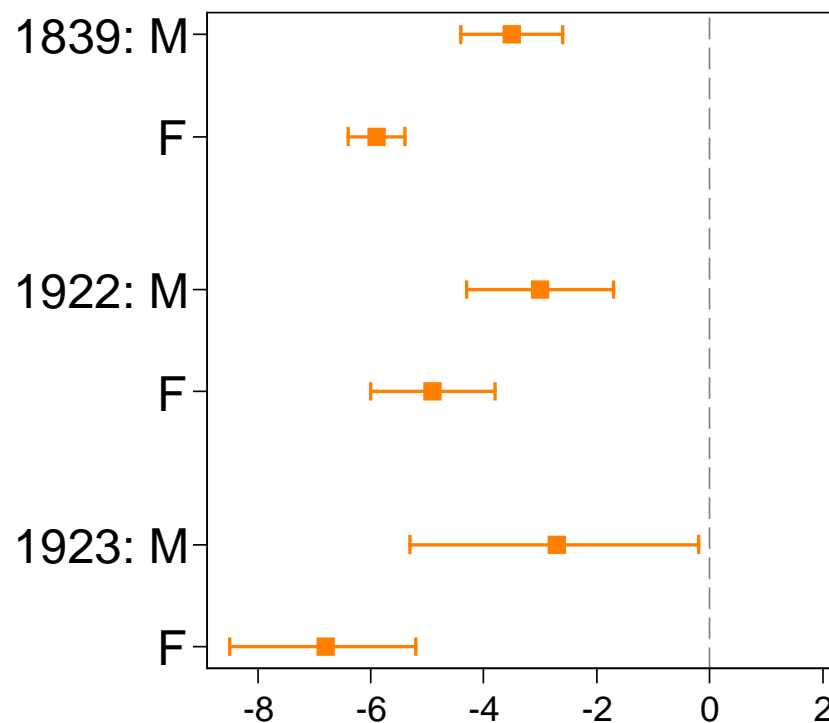
Results: Trial 1923

	Lira 3.0 mg Mean change	Placebo Mean change	Lira – Placebo (95% CI)
Fasting weight change (%)			
Weighted (ITT)	-5.0%	0.3%	-5.3% (-6.8, -3.8)
LOCF (FAS)	-6.1%	-0.1%	-6.1% (-7.5, -4.6)
	Lira 3.0 mg %	Placebo %	Lira - Placebo (95% CI)
Fasting weight reduction exceeds 5%			
Weighted (ITT)	44%	21%	23% (14, 31)
LOCF (FAS)	51%	22%	29% (20, 38)

Subgroup Analysis – Sex (FDA analysis)



Subgroup Analysis – Sex (LOCF w/ LAO-OT)



Fasting weight change (%)
Lira 3.0 mg - Placebo

Conclusions

- Concern that the sponsor's primary analysis exaggerates the treatment effect at week 56
- FDA analysis better reflects the treatment effect at week 56

References

National Research Council (2010). *The Prevention and Treatment of Missing Data in Clinical Trials*. Panel on Handling Missing Data in Clinical Trials. Committed on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press.

Carpenter, J., and Kenward, M. (2013). *Multiple imputation and its Application*. United Kingdom: Wiley.

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Analysis of Cancer Incidence Observed in Clinical Trials
of Liraglutide

Christian Hampp, PhD
CDER | OSE | OPE | Division of Epidemiology-I

This Presentation Includes

For thyroid, female breast, and colorectal cancer:

1. Internal comparisons

- Between patients randomized to liraglutide vs. comparator

2. External comparisons

- Between patients in liraglutide clinical trials and an external standard (U.S. SEER cancer incidence rates)

Methods

Sample

- Liraglutide weight management and diabetes programs
- Phase 2 and 3 trials
- Only comparator arms with drugs approved by FDA*
- Intent-to-treat with a preference for liraglutide
- Including extensions and observational follow-up
- Data cut-off: 120-day safety update

The sponsor provided age-, sex-, trial-, and exposure-specific follow-up times and counts of newly diagnosed neoplasms.

*different from analysis in sponsor's briefing document

Clinical Trial Pools

Pool	Description	Number of trials
1a	All weight management trials	5
→ 1b	Weight management trials (WM) with adjudication of cancer events	4
→ 2	All diabetes trials (DM)	25
→ 3	Combination of 1a and 2	30

- Analyses based on adjudicated events (WM) include only malignant neoplasms (and in situ breast neoplasms)
- All other analyses include non-adjudicated malignant or unspecified neoplasms

Methods – Internal Comparisons

- For each clinical trial pool: rate ratios (RR_{MH}) and rate differences (RD_{MH}) for thyroid, female breast, and colorectal cancer according to the Mantel-Haenszel method
 - stratified analysis that computes weighted averages across strata (trials), maintains the benefits of randomization, and accounts for different drug-comparator allocation ratios
- RR_{MH} for all reported cancers using only adjudicated events in the WM pool (Pool 1b) and non-adjudicated malignant and unspecified events in all liraglutide trials (Pool 3)
- Clinical trials with zero events of a cancer of interest were included in calculations of RD_{MH} but not in calculations of RR_{MH}

Methods – External Comparisons

- Comparison of cancer incidence rates **observed** in clinical trials to **expected** incidence rates based on U.S. population level data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database (2007 through 2011)
- Exposure-specific standardized incidence ratios (SIRs) summarize observed vs. expected event counts using age- and sex-standardization

Results

Internal Comparisons Between Patients Randomized to Liraglutide vs. Comparator

Internal Comparison – Thyroid Neoplasm

Pool		Both Sexes	
Adjudicated		Liraglutide	Comparator
1b (WM)	Events, n	4	1
	Pt-years	4,766.2	2,286.9
	RR _{MH}	1.90	
	95% CI	0.27-13.35	
	RD _{MH}	4.50	
MedDRA*			
1b (WM)	Events, n	15	4
	Pt-years	4,766.2	2,286.9
	RR _{MH}	1.86	
	95% CI	0.63-5.45	
	RD _{MH}	15.28	
2 (DM)	Events, n	46	6
	Pt-years	6,747.2	2,028.4
	RR _{MH}	2.03	
	95% CI	0.86-4.78	
	RD _{MH}	34.44	

RD_{MH} per 10,000 patient-years

*MedDRA-based cases include malignant and unspecified neoplasms

Internal Comparison

– Female Breast Neoplasm (not including *in situ*)

Pool		Females	
Adjudicated		Liraglutide	Comparator
1b (WM)	Events, n	12	2
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.98	
	95% CI	0.69-12.81	
	RD _{MH}	24.34	
MedDRA*			
1b (WM)	Events, n	13	3
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.07	
	95% CI	0.60-7.15	
	RD _{MH}	19.64	
2 (DM)	Events, n	9	1
	Pt-years	3,028.3	856.8
	RR _{MH}	1.52	
	95% CI	0.17-13.36	
	RD _{MH}	6.87	

RD_{MH} per 10,000 patient-years

*MedDRA-based cases include malignant and unspecified neoplasms

Internal Comparison

– *in situ* Female Breast Neoplasm

Pool		Females	
Adjudicated		Liraglutide	Comparator
1b (WM)	Events, n	3	1
	Pt-years	3,442.5	1,669.2
	RR _{MH}	1.39	
	95% CI	0.15-13.40	
	RD _{MH}	2.42	
MedDRA*			
1b (WM)	Events, n	4	1
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	6.69	
2 (DM)	Events, n	0	0
	Pt-years	3,028.3	856.8
	RR _{MH}	--	
	95% CI	--	
	RD _{MH}	0	

RD_{MH} per 10,000 patient-years

*MedDRA-based cases include malignant and unspecified neoplasms

Internal Comparison – Colorectal Neoplasm



Pool		Both Sexes	
Adjudicated		Liraglutide	Comparator
1b (WM)	Events, n	2	1
	Pt-years	4,766.2	2,286.9
	RR _{MH}	0.82	
	95% CI	0.07-9.90	
	RD _{MH}	-0.81	
MedDRA*			
1b (WM)	Events, n	2	0
	Pt-years	4,766.2	2,286.9
	RR _{MH}	--	
	95% CI	--	
	RD _{MH}	3.68	
2 (DM)	Events, n	8	3
	Pt-years	6,747.2	2,028.4
	RR _{MH}	1.05	
	95% CI	0.27-4.01	
	RD _{MH}	0.74	

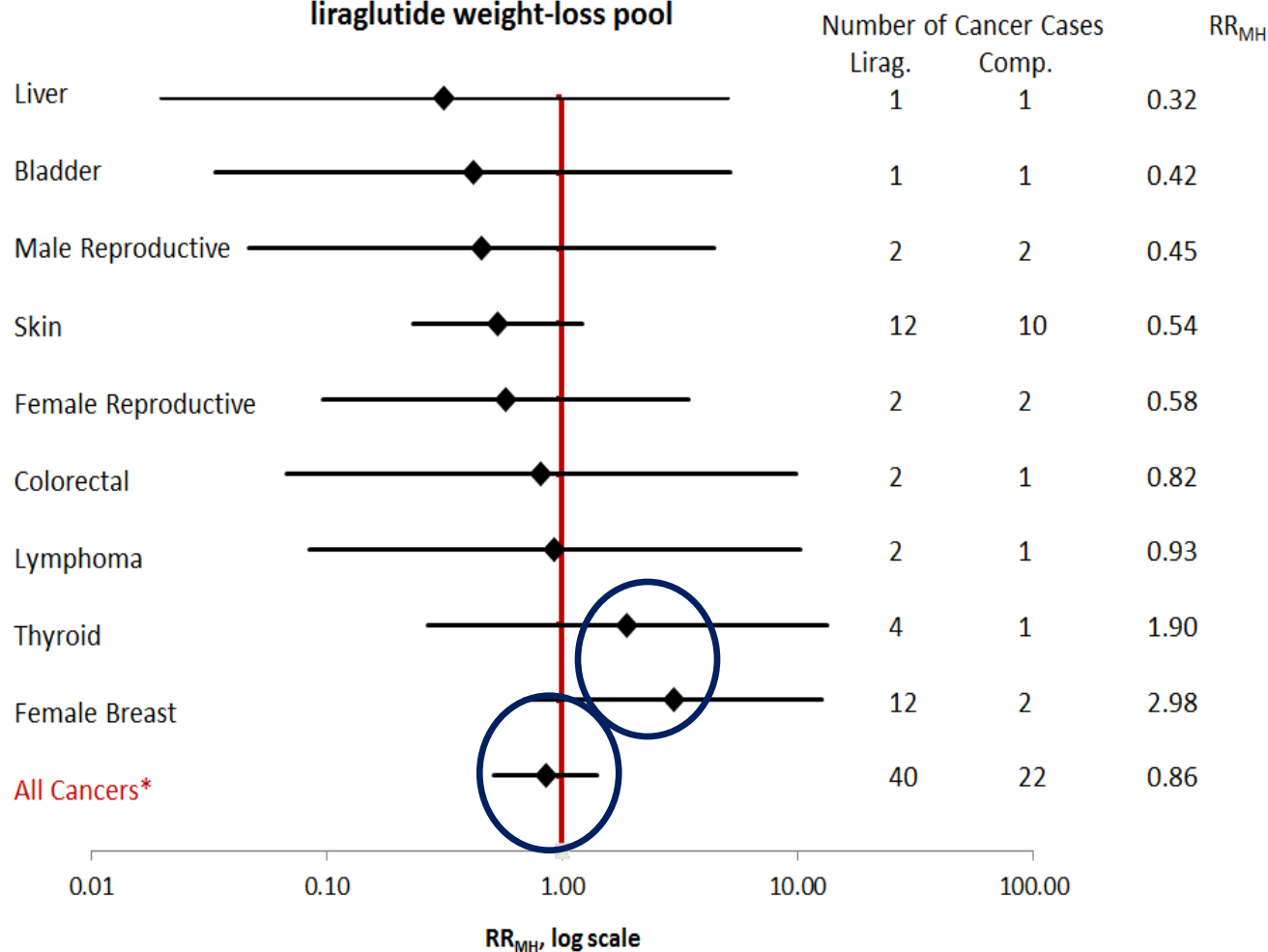
RD_{MH} per 10,000 patient-years

*MedDRA-based cases include malignant and unspecified neoplasms

Internal Comparison

– All Malignant Neoplasms

Mantel-Haenszel adjusted rate ratios for adjudicated malignant neoplasms observed in the liraglutide weight-loss pool

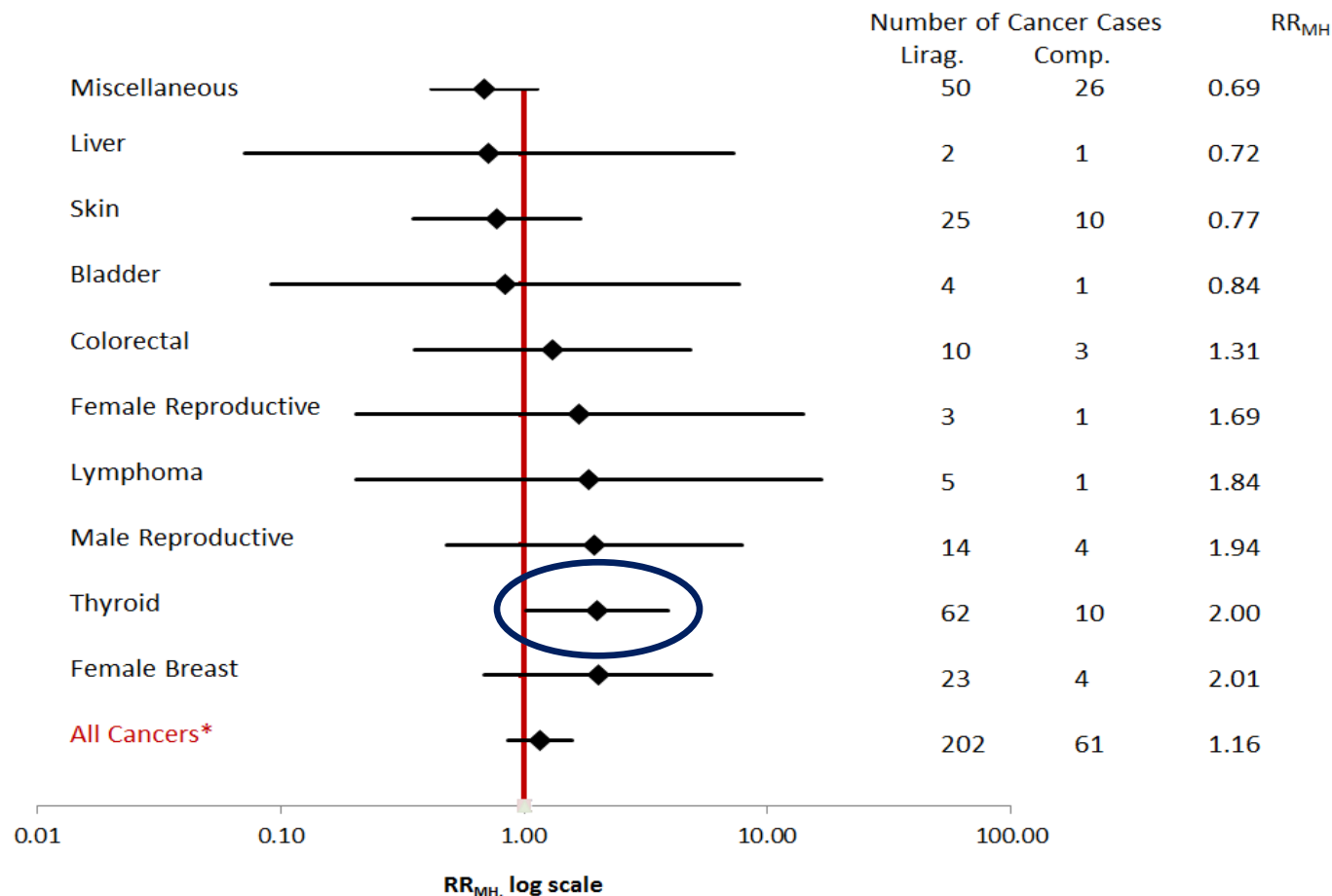


*All Cancers counts include cancer types with zero cases among either liraglutide or comparator arms, which are not listed as individual cancer types. Thus, counts for All Cancers exceed the sum for the listed individual cancer types.

Internal Comparison

– All Neoplasms (Pool 3)

**Mantel-Haenszel adjusted rate ratios for malignant and unspecified neoplasms (MedDRA)
observed in the liraglutide weight-loss and diabetes pool**



*All Cancers counts include cancer types with zero cases among either liraglutide or comparator arms, which are not listed as individual cancer types. Thus, counts for All Cancers exceed the sum for the listed individual cancer types.

Results

External Comparisons

Between Patients in Liraglutide Clinical Trials and U.S. SEER Cancer Data

External Comparison – Thyroid Neoplasm

Pool		Both Sexes	
Adjudicated		Liraglutide	Comparator
1b (WM)	n(obs.)	4	1
	n(exp.)	1.17	0.56
	SIR	3.43	1.78
	95% CI	1.09-8.27	0.09-8.80
MedDRA*			
1b (WM)	n(obs.)	15	4
	n(exp.)	1.17	0.56
	SIR	12.85	7.14
	95% CI	7.47-20.73	2.27-17.21
2 (DM)	n(obs.)	46	6
	n(exp.)	1.44	0.42
	SIR	31.91	14.17
	95% CI	23.63-42.19	5.74-29.47

*MedDRA-based cases include malignant and unspecified neoplasms

External Comparison – Female Breast Neoplasm(not including *in situ*)

Pool		Females	
Adjudicated		Liraglutide	Comparator
1b (WM)	n(obs.)	12	2
	n(exp.)	6.23	3.02
	SIR	1.92	0.66
	95% CI	1.04-3.27	0.11-2.19
MedDRA*			
1b (WM)	n(obs.)	13	3
	n(exp.)	6.23	3.02
	SIR	2.09	0.99
	95% CI	1.16-3.48	0.25-2.70
2 (DM)	n(obs.)	9	1
	n(exp.)	8.14	2.39
	SIR	1.11	0.42
	95% CI	0.54-2.03	0.02-2.07

*MedDRA-based cases include malignant and unspecified neoplasms

External Comparison – -in situ Female Breast Neoplasms

Pool		Females	
Adjudicated		Liraglutide	Comparator
1b (WM)	n(obs.)	3	1
	n(exp.)	1.78	0.87
	SIR	1.69	1.16
	95% CI	0.43-4.59	0.06-5.70
MedDRA*			
1b (WM)	n(obs.)	4	1
	n(exp.)	1.78	0.87
	SIR	2.25	1.16
	95% CI	0.72-5.43	0.06-5.70
2 (DM)	n(obs.)	0	0
	n(exp.)	2.25	0.65
	SIR	--	--
	95% CI	--	--

*MedDRA-based cases include malignant and unspecified neoplasms

External Comparison –Colorectal Neoplasm

Pool		Both sexes	
Adjudicated		Liraglutide	Comparator
1b (WM)	n(obs.)	2	1
	n(exp.)	2.25	1.03
	SIR	0.89	0.97
	95% CI	0.15-2.93	0.05-4.79
MedDRA*			
1b (WM)	n(obs.)	2	0
	n(exp.)	2.25	1.03
	SIR	0.89	--
	95% CI	0.15-2.93	--
2 (DM)	n(obs.)	8	3
	n(exp.)	5.65	1.74
	SIR	1.42	1.72
	95% CI	0.66-2.69	0.44-4.69

*MedDRA-based cases include malignant and unspecified neoplasms

Discussion and Conclusions

Factors That Can Lead to Higher Cancer Rates in Trials Compared with SEER Data:

- Association of diabetes and obesity with increased risk of certain cancer types, including thyroid cancer, breast cancer, and colorectal cancer
- Surveillance bias due to regularly scheduled follow-up visits
- Detection bias related to labeling of liraglutide for thyroid C-cell tumors
- Detection bias due to drug effects (e.g. weight loss can facilitate detection of breast cancer; in fact, SIRs for breast cancer were higher in weight-loss than in diabetes pools)
- Inclusion of non-adjudicated events (MedDRA)
- Inclusion of both malignant and unspecified events in analyses based on MedDRA search terms, while U.S. SEER data only include malignant neoplasms
- Differences in cancer rates for international trial participants compared to U.S. population captured in SEER data

Factors That Can Lead to **Lower** Cancer Rates in Trials Compared with SEER Data:

- Voluntary participation can result in the selection of healthier patients with higher socioeconomic status and better access to healthcare and prevention
- Inclusion and exclusion criteria may result in a sample at lower risk for cancer
- Differences in cancer rates for international trial participants compared to U.S. population captured in SEER data

Conclusions I

Internal comparisons:

- possibility of increased risk for thyroid cancer and female breast cancer associated with liraglutide
- rate ratios for all cancers grouped together were not increased and several cancer types occurred less frequently with liraglutide
- not unexpected in a multiple testing situation even in the absence of a treatment effect
- limited time between first exposure to the study drug and cancer diagnosis may not allow for the detection of a cancer initiating effect
- data can neither confirm nor exclude a causal role of liraglutide in the etiology of thyroid and female breast cancer

Conclusions II

External comparisons:

- In the clinical trial program of liraglutide, thyroid cancers occurred somewhat more frequently than what would be expected in an age- and sex-standardized U.S. population.
- This was not the case for other cancers to this extent.
- Comparisons between clinical trial data and a reference population should be carefully interpreted.

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FDA-Reviewed Observational Studies on GLP-1 Analogs

Christian Hampp, PhD
CDER | OSE | OPE | Division of Epidemiology-I

This Presentation Includes

An overview of published observational studies on glucagonlike-peptide-1 (GLP-1) analogs that were reviewed by FDA epidemiologists:

- Exenatide, liraglutide, and acute pancreatitis
- Exenatide, liraglutide, and thyroid and pancreatic cancer

Briefly:

- Studies that were not reviewed in-depth by FDA

Ongoing postmarketing requirements (PMR):

- Medullary Thyroid Carcinoma (MTC) registry for GLP-1 analogs

This is not a systematic review of the literature.

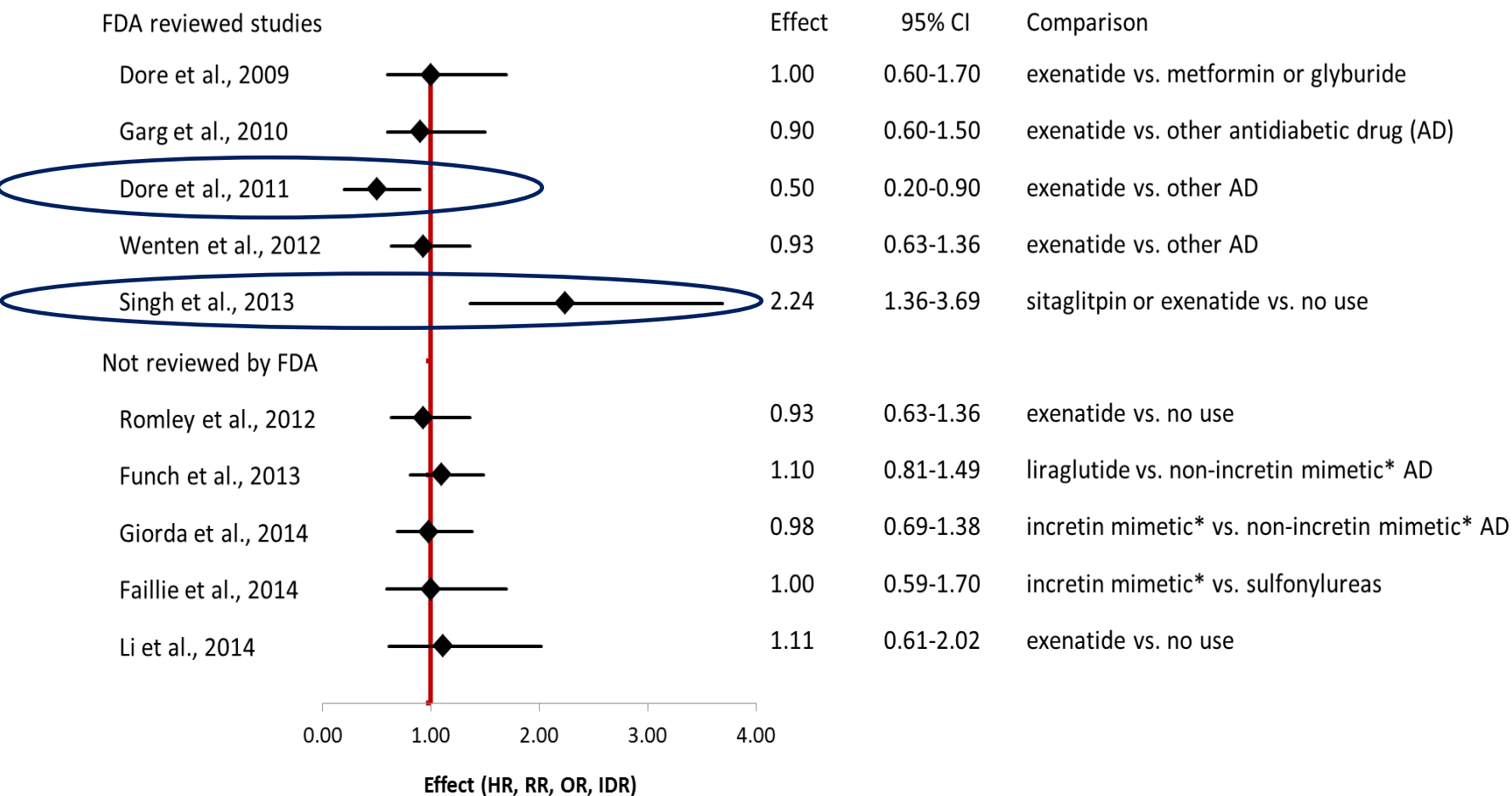
It does not include preclinical studies, clinical trials, studies based on spontaneous adverse events reporting, or unpublished observational studies.

GLP-1 Analogs and Acute Pancreatitis

GLP-1 Analogs and Acute Pancreatitis

- 10 published observational studies, 5 of which underwent in-depth review by FDA epidemiologists
- Forest Plot:
 - Plot includes relative effect measures as used in studies: hazard-, risk-, rate-, odds-, and incidence density ratios
 - When effect estimates for any, current, recent, or past use were presented, the plot includes either the estimate for current use or for any use if current use was not shown
 - No calculation of summary measure due to limited study quality

Published observational studies on glucagonlike-peptide-1 analogs and acute pancreatitis



*Incretin mimetics include glucagonlike-peptide-1 analogs and dipeptidyl-peptidase-4 inhibitors

Comments

- Only one study (Dore et al., 2011) included adjudication of acute pancreatitis events
- Other studies relied on algorithms with positive predictive values of ~ 42-82%
- Insufficient ascertainment of diabetes duration and severity, BMI, alcohol use, hypercholesterolemia, gallstones
- Comparator cohorts (initiators of other antidiabetic drugs) are highly diverse
- Insufficient power to examine hemorrhagic or necrotizing pancreatitis
- Studies conducted mostly in patients younger than 65

GLP-1 Analogs and Cancer

Dore et al., Therapeutic Advances in Drug Safety, 2012

- Cohort study, i3 Apero, 2005-2009
 - Thyroid neoplasm (malignant):
 - Exenatide vs metformin or glyburide: $RR_{adj} = 1.40$ (95% CI, 0.8-2.4)
 - Using inpatient thyroid malignancy claims: $RR_{adj} = 0.9$ (95% CI, 0.3–2.6)
 - Pancreatic cancer:
 - Exenatide vs metformin or glyburide: $RR_{adj} = 0.80$ (95% CI, 0.5-1.6)
- Limitations:
 - No endpoint adjudication
 - Insufficient covariate ascertainment
 - Limited sample size
 - Brief observation period

Studies Not Reviewed In-depth by FDA

- Romley et al., Diabetes Technology and Therapeutics, 2012
 - Pancreatic malignancy:
 - Exenatide vs. no exenatide (?): **OR_{adj} = 1.54** (95% CI, 0.49-4.87)
- Funch et al., Diabetes, Obesity and Metabolism, 2013
 - Pancreatic malignancy:
 - Liraglutide vs. non-incretin antidiabetic: **RR_{adj} = 0.65** (95% CI, 0.26-1.60)
- **None of these studies included event adjudication**

Study Limitations

- No event adjudication
- Insufficient ascertainment of diabetes severity, BMI, alcohol use, family history of cancer, environmental/occupational exposures
- Insufficient power resulted in imprecise effect estimates
- Observation periods too brief to assess long-latency outcomes
- Studies conducted mostly in patients younger than 65

Ongoing Post-Marketing Requirements (PMR)

- Pancreatic cancer and thyroid neoplasm with exenatide (PMR #1559-8)
- Thyroid cancer and serious hypoglycemia, pancreatitis, hypersensitivity, and overall malignant neoplasms with liraglutide (PMR #1583-6)

MTC Registry for GLP-1 Analogs

MTC Registry

- A medullary thyroid carcinoma case series registry of at least 15 years duration is being required from all manufacturers of long-acting GLP-1 analogs
- Conducted by United BioSource Corporation on behalf of MTC Registry Consortium
- As of January 2014, 13 cases of MTC have been captured by the MTC registry; none of the patients have been exposed to GLP-1 receptor agonists*
- FDA is monitoring annual interim reports

* Novo Nordisk briefing document for September 11, 2014 EMDAC mtg, p.180.

Conclusions

Acute Pancreatitis

- Observational studies have not provided substantive evidence for an increased risk of acute pancreatitis associated with GLP-1 analogs, and are subject to important limitations

Thyroid Cancer and Pancreatic Malignancy

- Observational studies show mixed results for the association between GLP-1 analogs and thyroid and pancreatic cancer, but are subject to substantial limitations

MTC Registry

- Sufficient recruitment of MTC patients is critical for success of registry
- Even if observed, it will be difficult to attribute increase in MTC diagnoses to GLP-1 agonist exposure

References

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- Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010 Nov;33(11):2349-54.

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- Li X, Zhang Z, Duke J. Glucagon-like peptide 1-based therapies and risk of pancreatitis: a self-controlled case series analysis. *Pharmacoepidemiol Drug Saf*. 2014 Mar;23(3):234-9.
- Romley JA, Goldman DP, Solomon M, et al. Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. *Diabetes Technol Ther*. 2012 Oct;14(10):904-11.
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Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Hyattsville, MD
September 11, 2014

Victoza®

Postmarketing Serious Adverse Events Reported to the
FDA Adverse Event Reporting System (FAERS)

Debra Ryan, PharmD, MBA
CDER|OSE|OPE|Division of Pharmacovigilance I

Presentation Purpose

- Overview of spontaneous reporting
- Regulatory actions supported by spontaneous reports identified postmarketing
- Overview of the serious adverse event postmarketing safety profile of Victoza®
- FAERS reports for events of special interest
- FAERS reports of Medullary Thyroid Cancer (MTC) associated with Victoza®

Spontaneous Adverse Event Reporting

- FDA has collected spontaneous adverse drug event since 1960s
 - Mandatory reporting by manufacturers
 - Voluntary reporting by healthcare professionals, patients, and the general public
- FAERS – Current database
 - Over 9 million reports
 - US and foreign sources
 - Ongoing large-scale surveillance in “real world”
 - Provides early signal detection
 - Rare events that clinical trials are not powered to detect

Limitations of Spontaneous Reporting

- Underreporting
- Stimulated reporting
- Prevalence of an event in the untreated population
- Confounding co-morbidities
- Latency
- Reporting Biases

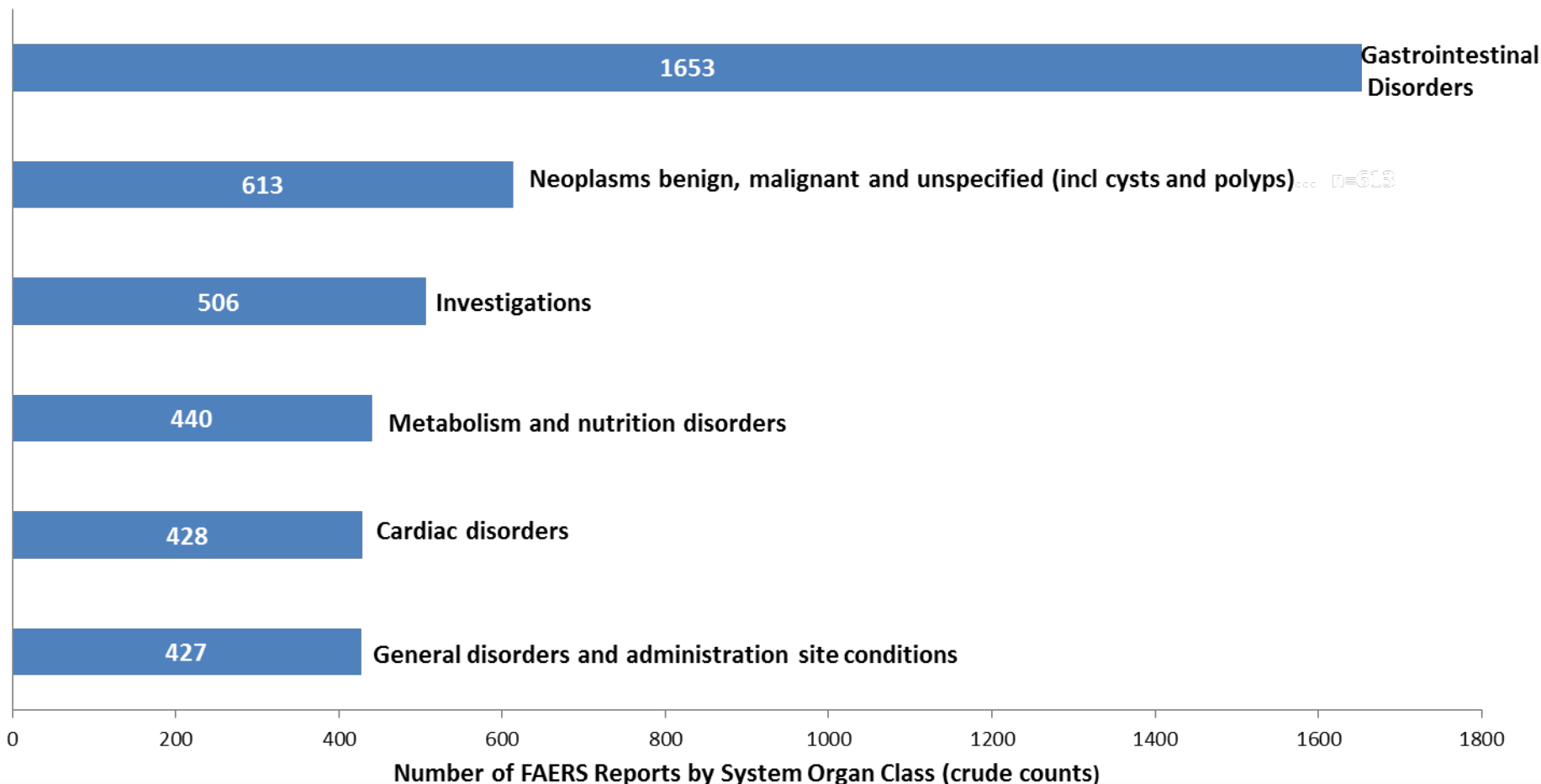
Postmarketing Regulatory Actions Supported by Spontaneous Reports

- Acute Renal Failure: May 18, 2011*
- Anaphylaxis & Hypersensitivity Reactions: April 6, 2012*
- Pancreatitis: April 16, 2013*
- Medication Errors: June 13, 2013*

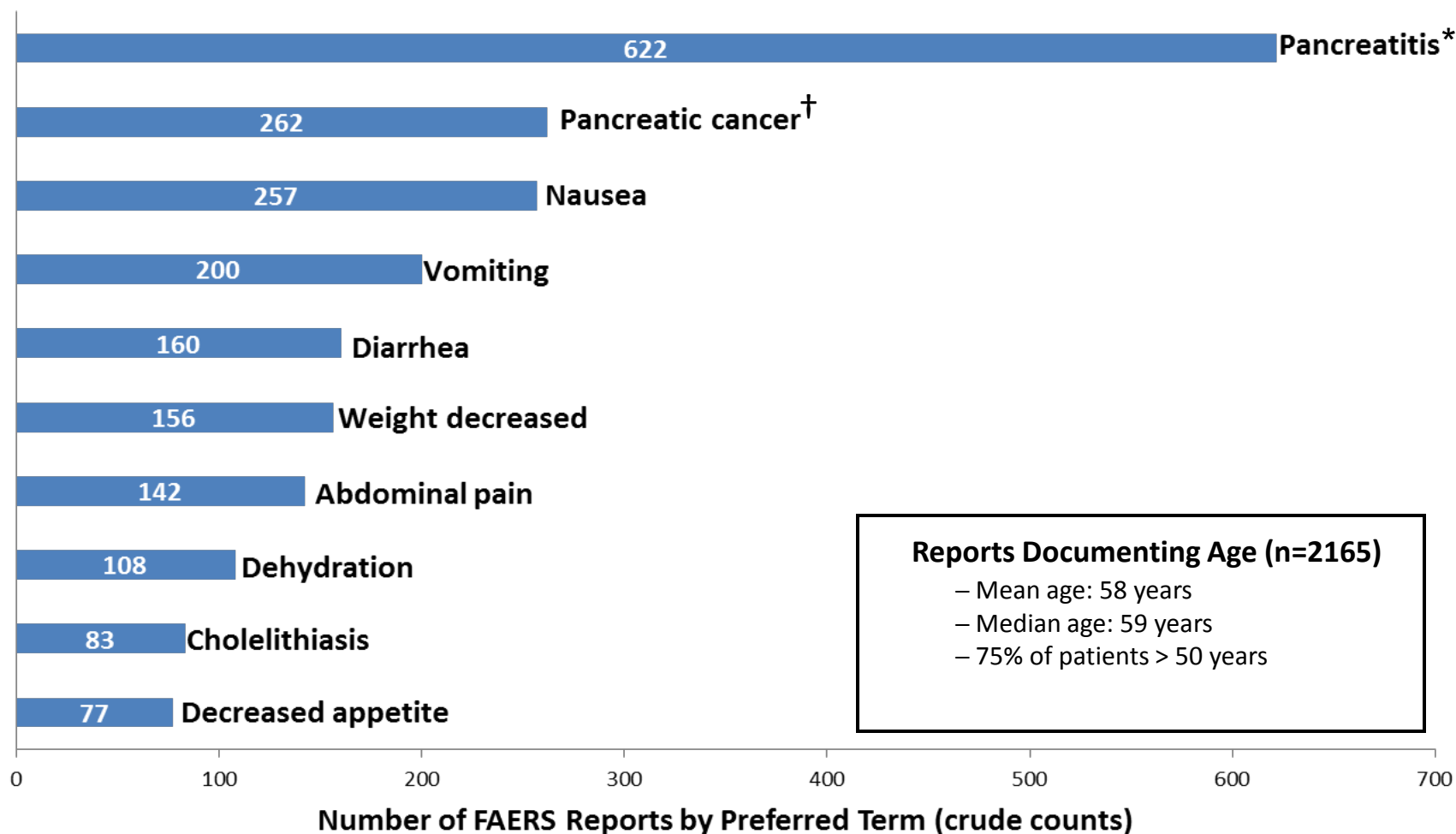
*Date supplemental new drug application was approved by the FDA

Overview of FAERS Data for Victoza®

- Total number of reports >15,000
- Adverse events reporting a serious outcome (n=3,110)
- FAERS reports by System Organ Class (SOC)



Top Ten Reported Preferred Terms



*Pancreatitis & Pancreatitis acute †Pancreatic carcinoma, Pancreatic carcinoma metastatic, Pancreatic neoplasm, Adenocarcinoma pancreas

Saxenda Clinical Program Events of Special Interest

- **Gallbladder**
 - ✓ Confounding Co-morbidities
- **Cardiovascular**
 - ✓ Confounding Co-morbidities & Prevalent Event in Population
- **Neuropsychiatric**
 - ✓ Confounding Co-morbidities & Prevalent Event in Population
- **Breast Cancer**
 - ✓ Latency & Prevalent Event in Population
- **Pancreatic Cancer**
 - ✓ Latency, Prevalent Event in Population, & Stimulated Reporting
- **Thyroid Cancer** (not including Medullary Thyroid Cancer)
 - ✓ Latency, Prevalent Event in Population, & Stimulated Reporting

Summary

- Postmarketing Safety Issues identified in FAERS addressed through Product Labeling
 - Pancreatitis, acute renal failure, anaphylaxis & hypersensitivity reactions, and medication errors due to injection technique
- Postmarketing Safety Event of Concern
 - MTC
- FAERS Strengths
 - Rare event

Rare, Serious, Currently Unlabeled Event: Human Cases of MTC

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)*].

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Hyattsville, MD
September 11, 2014

**Spontaneously Reported
Medullary Thyroid Cases
in
FDA Adverse Event Reporting System (FAERS)**

Marina Zemskova, M.D.
Medical Officer
Division of Metabolism and Endocrinology Products
Office of New Drugs
CDER

Thyroid Cancer

- Thyroid cancer represents 3.8% of all new cancer cases in the U.S. and is the most common endocrine malignancy*
- There are four types of thyroid cancer
 - papillary -70-80%
 - follicular -10-15%
 - medullary -3-10%
 - anaplastic < 5%

*Surveillance, Epidemiology, and End Results (SEER) program

Basics: Medullary Thyroid Cancer (MTC)

- Rare malignancy
- Incidence rate 0.22 per 100,000 person-years*
- Arises from parafollicular cells (C-cells)
- Sporadic MTC-80%
 - Typical age of presentation is in 5th or 6th decade
- Familial MTC -20%
 - MEN2a, MEN2b, familial medullary cancer
 - Germline mutation in RET proto-oncogene

*Aschebrook-Kilfoy B et al. Thyroid cancer incidence patterns in the United States by histologic type, 1992-2006. *Thyroid*. 2011 Feb;21(2):125-34

Typical MTC Presentation at Time of Diagnosis

- 75-95% of patients detected because of solitary nodule
- 50% of patients have cervical lymph node metastasis
- 5% of patients have distant metastasis

MTC and C-cell Hyperplasia Cases in FAERS

- 13 cases of MTC
 - 9 reports from US
 - 3 reports from Europe (2-France, 1-Belgium)
 - 1 report from Canada
- Demographic characteristics of patients with MTC
 - Majority of patients > 50 years old (age range 43-78 years)
 - 4 males : 9 females
- 4/13 cases –had no clinical information available
- 9 cases with some clinical data will be discussed

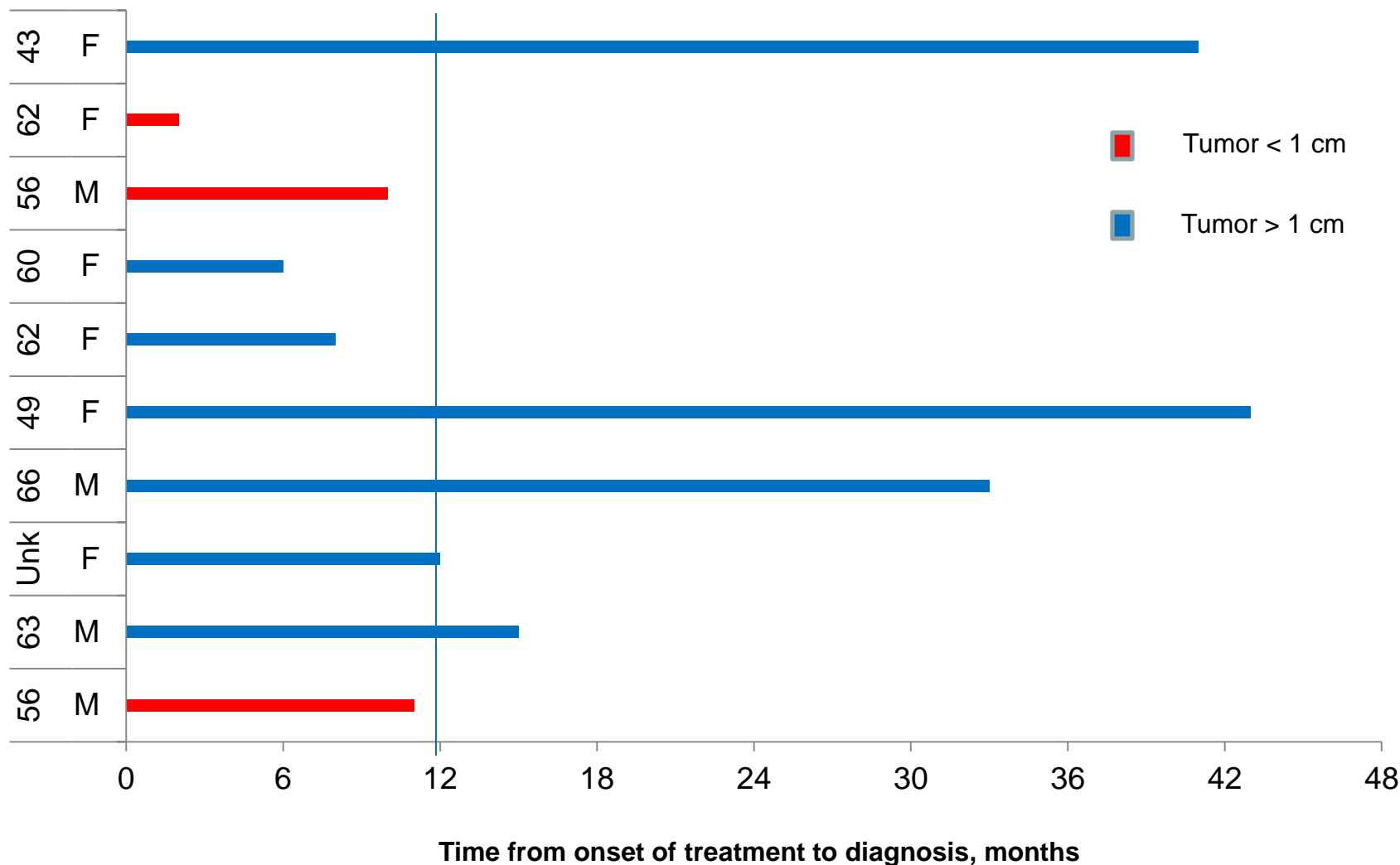
Evaluation Prior to Exposure

Immediately Prior to Initiation of Liraglutide Therapy

- No clinical information about ultrasound or FNA reported for any cases
 - 2 patients had a remote history of goiter and one patient had an FNA which revealed benign pathology in the past
- No clinical information about calcitonin levels reported for any cases
- No clinical information about RET genetic testing reported
- Information about history of MEN2 or familial MTC
 - 7/9 patients – asked and denied history
 - 2/9 patient –family history not available on the reports
- Prior exposure to other GLP-1 agonists
 - 1 patient treated with exenatide (Byetta) for 4 years

Exposure Prior to Diagnosis

Age, sex



Initial Presentation

Age/Sex, Country	Time from first exposure to diagnosis (months)	Reason for Workup	Surgical Pathology
63/M, Belgium	15	Evaluation of liver, bone, lung metastasis	MTC
60/F, France	6	Palpable thyroid nodule	Not done
49/F, US	43	Palpable thyroid nodule	MTC 2.1 cm
43/F, US	41	Palpable thyroid nodule	Not done
56 /M, US	11	Ultrasound for hyperparathyroidism	MTC 0.1 cm PTC 0.1 cm
62/F, US	8	CT scan for unknown reason	MTC; “tiny” focus of PTC
66/M, US	33	CT scan for colon cancer	MTC 4.4 cm
56/M, France	11	Presence of goiter prior to the onset of treatment with liraglutide	MTC 0.3 cm
62/F, US	2	None, incidental finding during the surgery	MTC 0.3 cm PTC 0.1 cm

MTC Diagnosis

Age/Sex	Time from first exposure to diagnosis (months)	Ultrasound Report	FNA Report	Preoperative Calcitonin Levels (pg/ml)	RET Testing	Surgical Pathology Report
60/F	6	Unknown	MTC	1500	Unknown	Not done
62/F	8	1.6 cm thyroid nodule	MTC	170	Negative	MTC, "tiny" focus of PTC
63/M	15	Left thyroid and paratracheal masses	MTC (lymph nodes, bones)	265	Negative	MTC of left thyroid lobe with lymph nodes involvement and distant metastasis
66/M	33	4.4 cm thyroid nodule	Done, no results reported		Negative	4.4 cm MTC with 1 positive lymph node
49/F	43	3.1 cm thyroid nodule	MTC	926	Not done	MTC 2.1 cm
43/F	41	Thyroid nodule (1.6 cm by CT scan)	MTC	345	Unknown	Not done
56/M	9	Unknown	Suspicious		Unknown	MTC 0.3 cm (biopsied thyroid nodule was benign)
56 /M	11	1 cm thyroid nodule	Not done	Not done	Not done	MTC 0.1 cm PTC 0.1 cm
62/F	2	Unknown	Not done		Negative	MTC 0.3 cm PTC 0.1 cm

Surgical Findings

Age/Sex	Time from first exposure to diagnosis (months)	Surgical pathology report	Stage
60/F	6	Not done	
43/F	41	Not done	
62/F	8	MTC, "tiny" focus of PTC	Stage I
56 /M	11	MTC 0.1 cm, PTC 0.1 cm	
62/F	2	MTC 0.3 cm, PTC 0.1 cm	
56/M	1	MTC 0.3 cm (biopsied thyroid nodule was benign)	
49/F	43	MTC 2.1 cm	Stage I T2N0
66/M	33	4.4 cm MTC with 1 positive lymph node (partial thyroidectomy)	Stage III T3N1a
63/M	15	MTC of left thyroid lobe with lymph nodes involvement and distant metastasis	Stage IV T4aN1bM1

Surgery was done in 7/9 patients

- Size of tumor was 0.1 cm - 4.4 cm (reported in 5/7 patients)
- 3 patients had microcarcinoma (< 1 cm)
- 1/7 patients had regional lymph node metastasis
- 1/7 patients had regional lymph node and distant metastasis

Conclusion

- Causality assessment between MTC and liraglutide complicated by
 - Low number of reported cases
 - Relatively short duration of treatment prior to diagnosis
 - Presentation appears consistent with what is expected in general population
 - Important clinical information is missing from case reports:
 - Baseline assessment (ultrasound, calcitonin)
 - Family and past medical history
 - RET genetic testing
 - Staging

Efficacy Additional Endpoints

Julie Golden, M.D.

Medical Officer

Division of Metabolism and Endocrinology Products

Office of New Drugs

CDER

56-Week Phase 3 Trials, Secondary Endpoints

Mean Treatment Difference at Week 56, LOCF (Lira 3 mg – Placebo)

	Trial 1923	Trial 1839	Trial 1922
HbA1c, percentage points	-0.3	-0.2	-0.9 / -0.7 (1.8 mg)
SBP, mmHg	-2.7	-2.8	-2.6
DBP, mmHg	-0.3	-0.9	-0.4
LDL-C, %	-3.3	-2.4	-2.2
HDL-C, %	+0.6	+1.9	+2.8
TG, %	-8.6	-9.3	-13.7
Waist circumference, cm	-3.5	-4.2	-3.2

Secondary endpoints were not incorporated in the study-wise multiplicity adjustment framework

Sleep Apnea

Trial 3970

- Patient Population
 - 359 patients with moderate and severe OSA unable or unwilling to use CPAP
 - 72% male, mean age 49 yrs, 74% white, mean BMI 30 kg/m²
- Design
 - 32-week duration
 - Primary endpoint: change in AHI at 32 weeks, lira 3 mg vs. placebo
- Primary result
 - Lira 3 mg -12 events/h vs. placebo -6 events/h, treatment difference -6 events/h, p=0.015
- Limitations
 - Single, 32-week trial
 - Relatively narrow patient population
 - Clinical relevance unclear
 - Clinically relevant change in AHI not established
 - Supportive secondary endpoints generally not different from placebo

Liraglutide for Weight Management Safety

Safety Profile

Victoza (liraglutide for type 2 diabetes) Prescribing Information

- Boxed Warning: thyroid C-cell tumors
- Warnings and Precautions: pancreatitis, serious hypoglycemia, renal impairment, hypersensitivity, lack of macrovascular outcomes
- Adverse Reactions: gastrointestinal symptoms, immunogenicity, injection site reactions, hypoglycemia, papillary thyroid carcinoma, bilirubin elevations, and heart rate increases
- Post-Marketing: dehydration, renal failure, angioedema/anaphylaxis, allergic reactions, pancreatitis

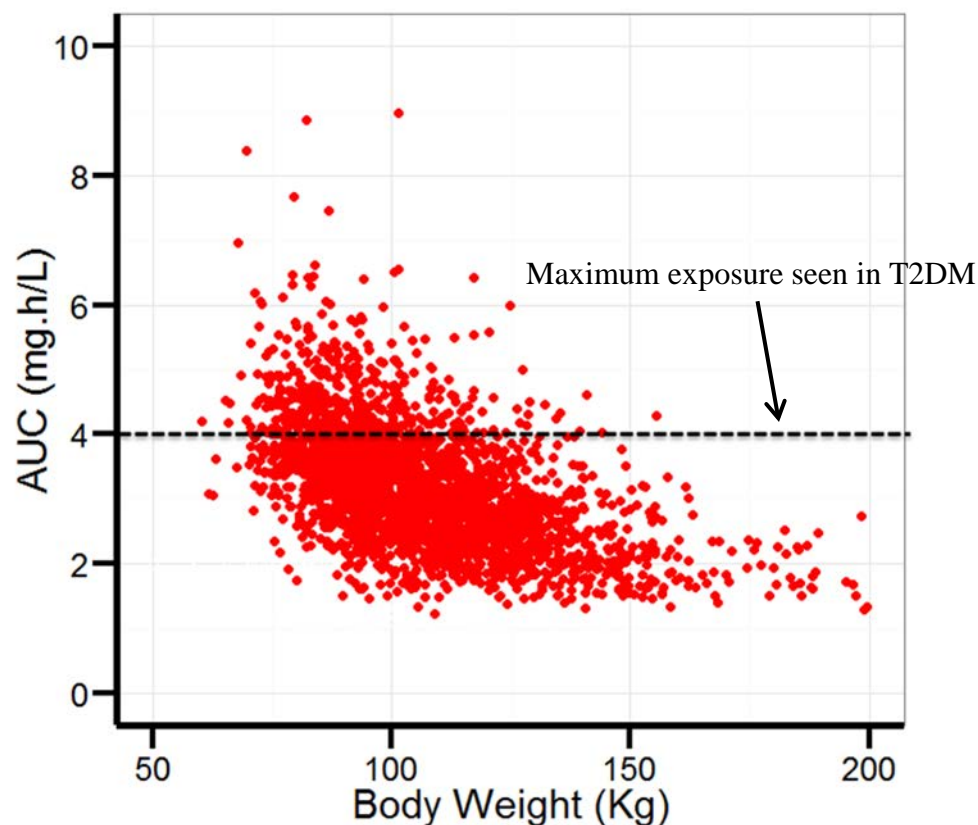
Safety Presentation

- Clinical trials
 - Dose considerations
 - Safety database
 - Serious adverse events (AEs)/ withdrawals / common AEs
 - Cardiovascular safety
 - Gallbladder disease / pancreatitis
 - Psychiatric safety
 - Neoplasms
- Post-marketing safety
 - Observational studies
 - FDA Adverse Event Reporting System
 - MTC case reports

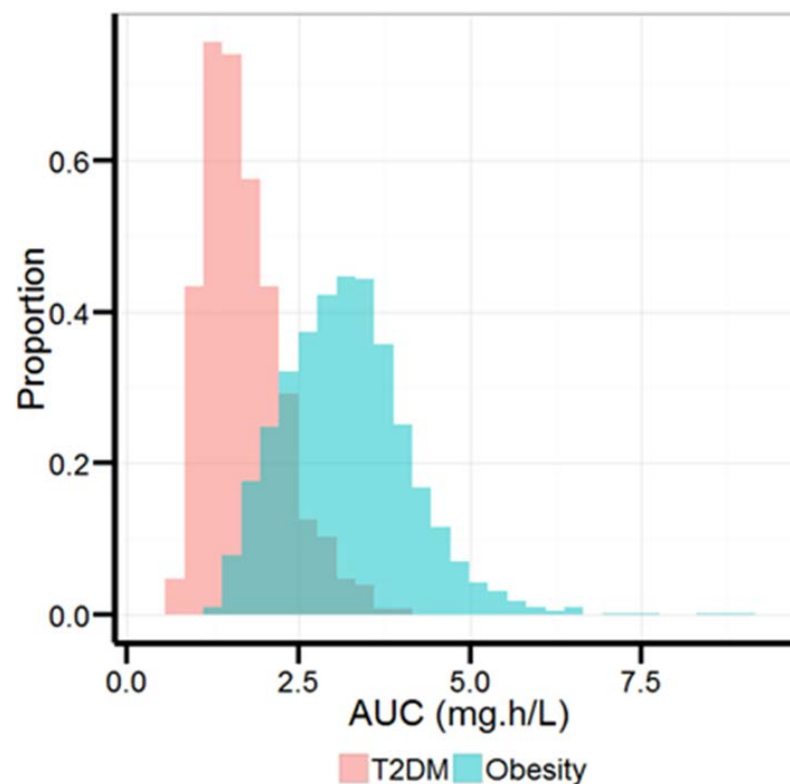
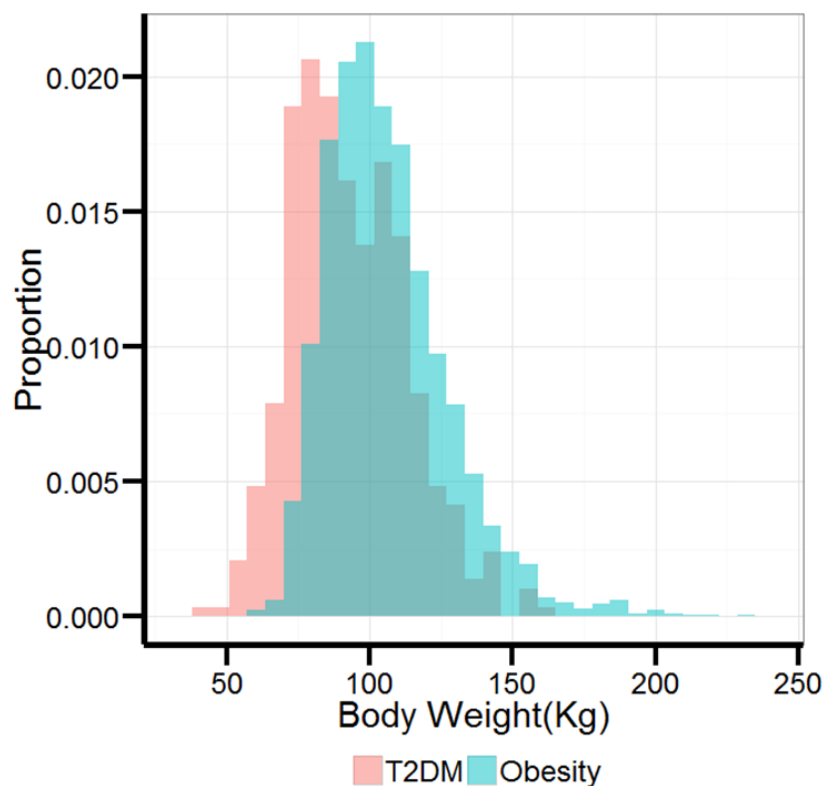
Dose Considerations

Body Weight Affects Liraglutide Pharmacokinetics

- Body weight is the most significant covariate affecting liraglutide clearance
- Therefore, patients with lower body weight are expected to have a higher liraglutide exposure (AUC) as compared to patients with higher body weight



Distribution of Body Weight (Left Panel) and Liraglutide Exposure (Right Panel) in T2DM & Obesity Programs



Liraglutide Clinical Trials Safety

Clinical Safety Database

- Weight management pool
 - 1807, 1923, 1839, 1922, 3970
 - Liraglutide 3 mg (N=3384) vs. placebo (N=1941)
 - Adjudicated neoplasms and pancreatitis (1923, 1839, 1922, 3970)
 - Adjudicated CV events and deaths (all 5 trials)
- Individual trials
 - Dose-response (1807, 1922)
 - Hypoglycemia (1922 – diabetes)
 - Heart rate (3630 – clinical pharmacology, 3970 – sleep apnea)
 - Longer-term data (1807, 1839 extensions)
- Diabetes pool
 - 24 trials, doses up to 1.8 mg
 - Comparators: sulfonylureas, metformin, TZDs, insulin, GLP-1 agonists, DPP-4 inhibitors, and placebo
 - No adjudication, except post hoc major adverse cardiovascular events (MACE)

Clinical Trial Exposure Weight Management Pool

	Lira 3 mg	Placebo
N	3384	1941
Patient-Years	2974	1601
Median exposure, yrs	1.1	1.1
≥ 3 mos exposure	3003 (89%)	1715 (88%)
≥ 6 mos exposure	2798 (83%)	1524 (79%)
≥ 12 mos exposure	2341 (69%)	1139 (59%)

- Ongoing 1839-ext exposure to liraglutide 3 mg :
 - 999 patients ≥ 18 mos
 - 906 patients ≥ 24 mos

SAEs, AEs Leading to Withdrawal, Common AEs

AE Summary

Weight Management Pool*

	Lira 3 mg N=3384	Placebo N=1941
Total AEs	3101 (91.6%)	1622 (83.6%)
Fatal AEs	1 (<0.1%)	3 (0.2%)
SAEs	213 (6.3%)	89 (4.6%)
AEs leading to withdrawal	331 (9.8%)	83 (4.3%)

*not including off-drug follow-up or extension periods

SAEs

Weight Management Pool

High Level Group Terms	Lira 3 mg N=3384	Placebo N=1941
Total SAEs	213 (6.3%)	89 (4.6%)
Gallbladder disorders	42 (1.2%)	6 (0.3%)
Joint disorders	13 (0.4%)	2 (0.1%)
Breast neoplasms, malignant and unspecified	8 (0.2%)	1 (<0.1%)
Uterine and pelvic disorders	8 (0.2%)	1 (<0.1%)
Gastrointestinal signs and symptoms	7 (0.2%)	1 (<0.1%)
Exocrine pancreas conditions	6 (0.2%)	0

Liraglutide > Placebo

AEs Leading to Withdrawal Weight Management Pool

Preferred Terms	Lira 3 mg N=3384	Placebo N=1941
Total AEs leading to withdrawal	331 (9.8%)	83 (4.3%)
Nausea	98 (2.9%)	4 (0.2%)
Vomiting	58 (1.7%)	1 (<0.1%)
Diarrhea	49 (1.4%)	0
Abdominal pain	21 (0.6%)	1 (<0.1%)
Constipation	17 (0.5%)	2 (0.1%)
Dizziness	15 (0.4%)	1 (<0.1%)
Fatigue	15 (0.4%)	1 (<0.1%)
Lipase increased	12 (0.4%)	3 (0.2%)

Liraglutide > Placebo

Common AEs

≥ 5%

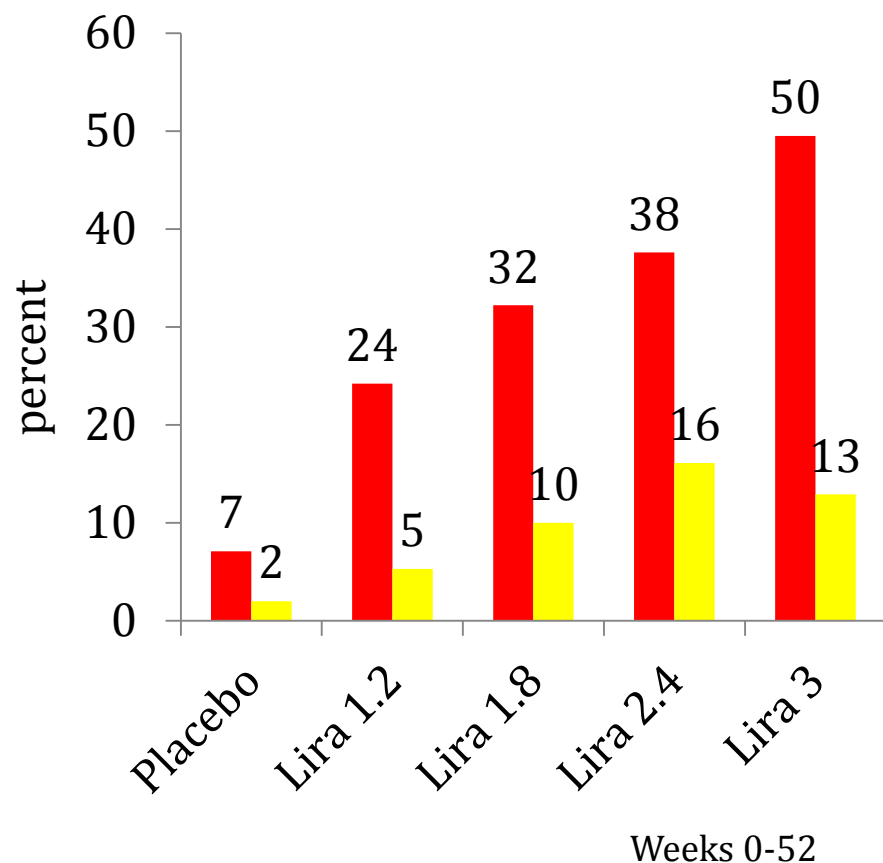
	Lira 3 mg N=3384	Placebo N=1941
Nausea	39%	14%
Diarrhea	21%	10%
Constipation	19%	9%
Vomiting	16%	4%
Hypoglycemia	15%	6%
Headache	14%	13%
Decreased appetite	10%	2%
Dyspepsia	10%	3%
Fatigue	8%	5%
Dizziness	7%	5%
Lipase increased	5%	2%
Abdominal pain	5%	3%
Abdominal pain upper	5%	3%

Liraglutide > Placebo

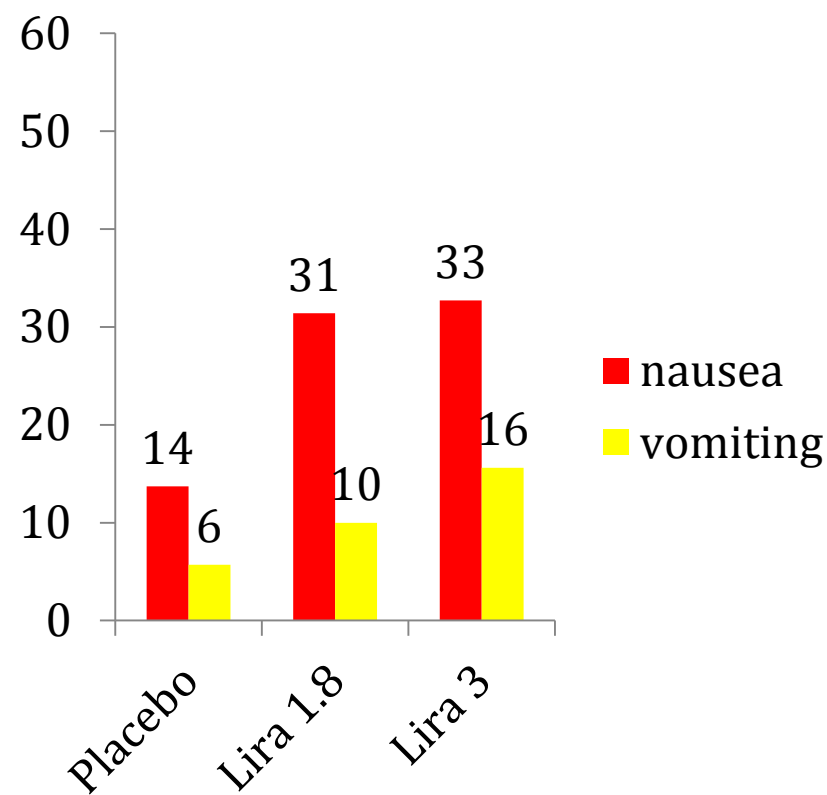
Nausea and Vomiting

By Dose

Trial 1807



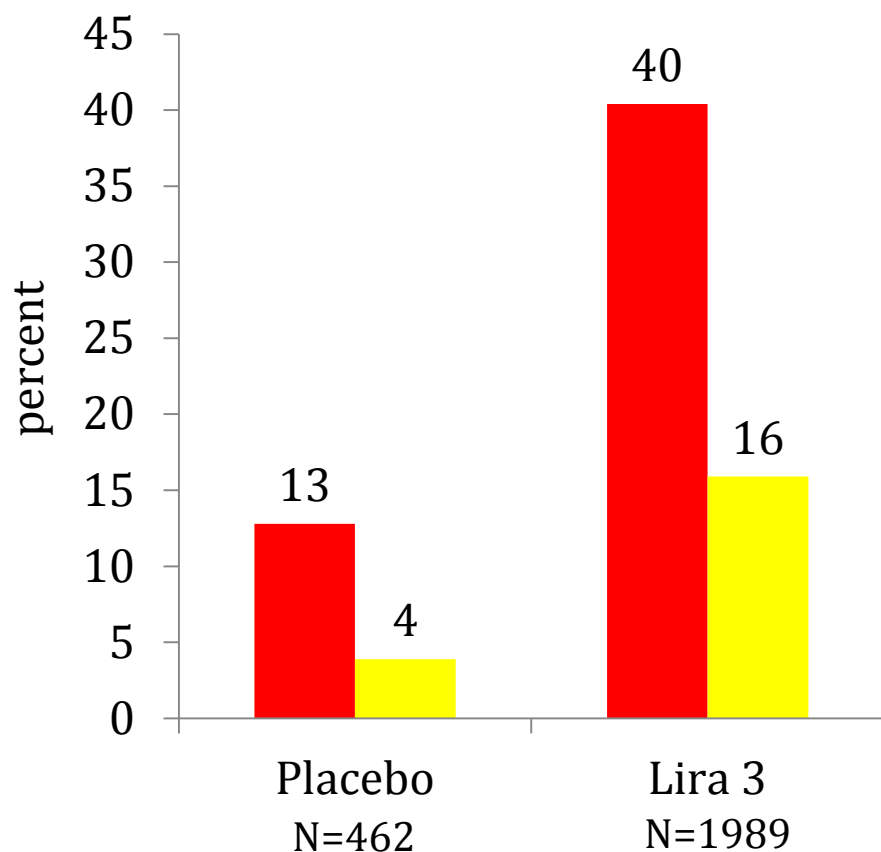
Trial 1922



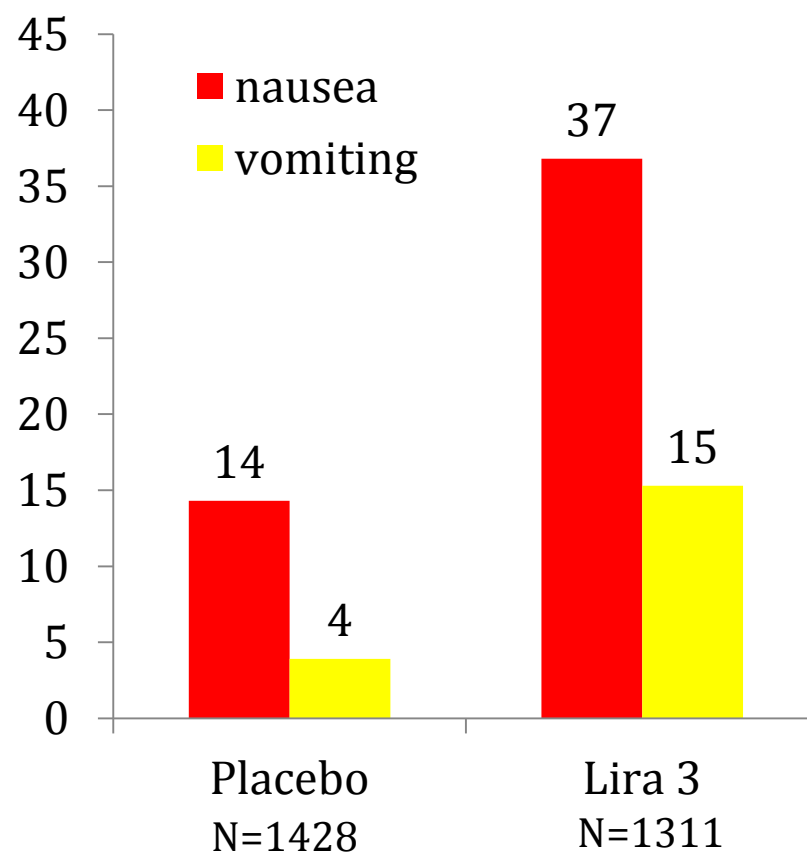
Nausea and Vomiting

By 5% Weight Loss Responder Status

Responders



Non-responders

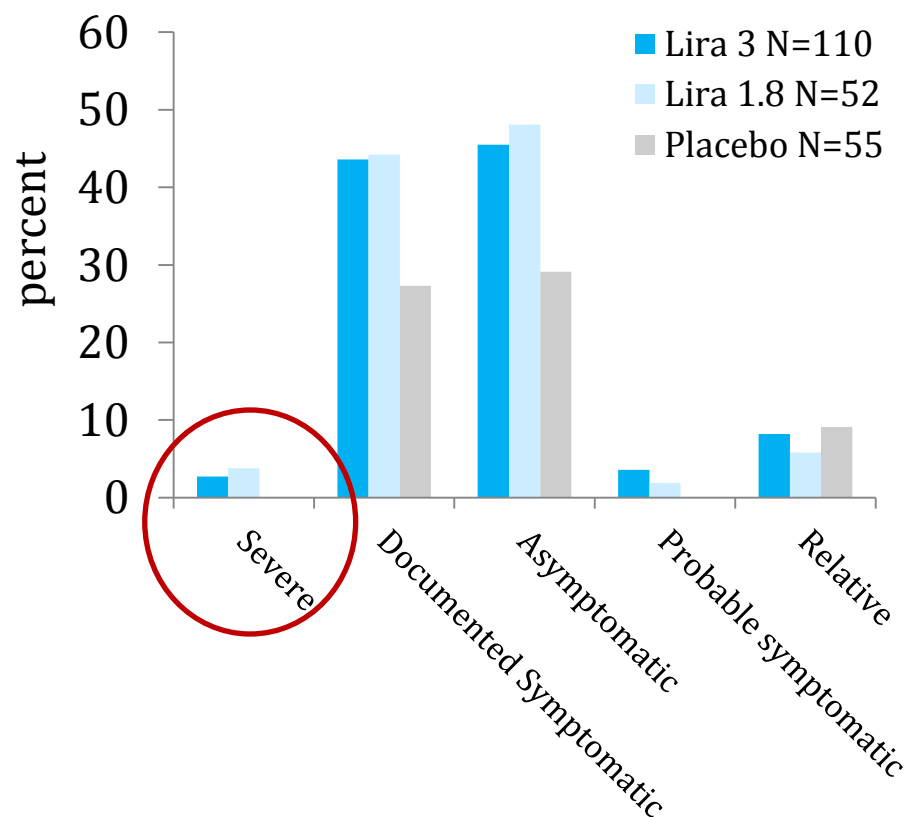


Nausea and Vomiting, General Comments

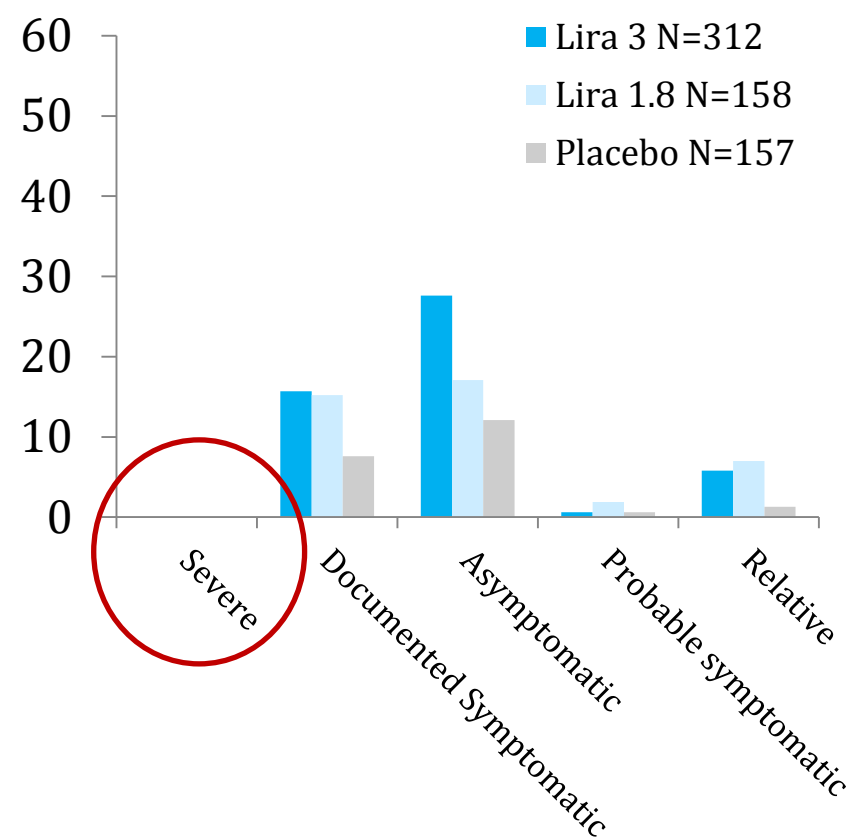
- Unblinding?
 - Efficacy: dietary / drug / study adherence
 - Reporter or ascertainment bias for AEs
- Effect on weight loss?
 - Imbalance noted in responders and non-responders
- Safety
 - Acute renal failure due to volume depletion
 - Patient 510002 / trial 1839 / 64 y F / history of renal impairment
 - Masking of serious AEs?

Hypoglycemia Trial 1922

On Background Sulfonylurea



Not on Background Sulfonylurea





Cardiovascular Safety

Sibutramine / SCOUT

- Sibutramine approved in 1997 for the management of obesity; withdrawn 2010
- Associated with:
 - Mean placebo-subtracted weight loss ~4%
 - Mean increases in blood pressure 1 to 3 mmHg vs. placebo
 - Mean increases in heart rate 4 to 5 bpm vs. placebo
- SCOUT: Sibutramine Cardiovascular Outcomes Trial¹
 - 10,000 overweight/obese patients with CV risk factors
 - Primary endpoint: first occurrence of non-fatal MI, non-fatal stroke, resuscitation after cardiac arrest or CV death
 - Mean treatment duration 3.4 years
 - Sibutramine 11.4%, placebo 10.0%; hazard ratio 1.16 (95% CI 1.03, 1.31), p=0.015

¹ James WP et al. N Engl J Med 2010;363:905-917

Look AHEAD (Action for Health in Diabetes)

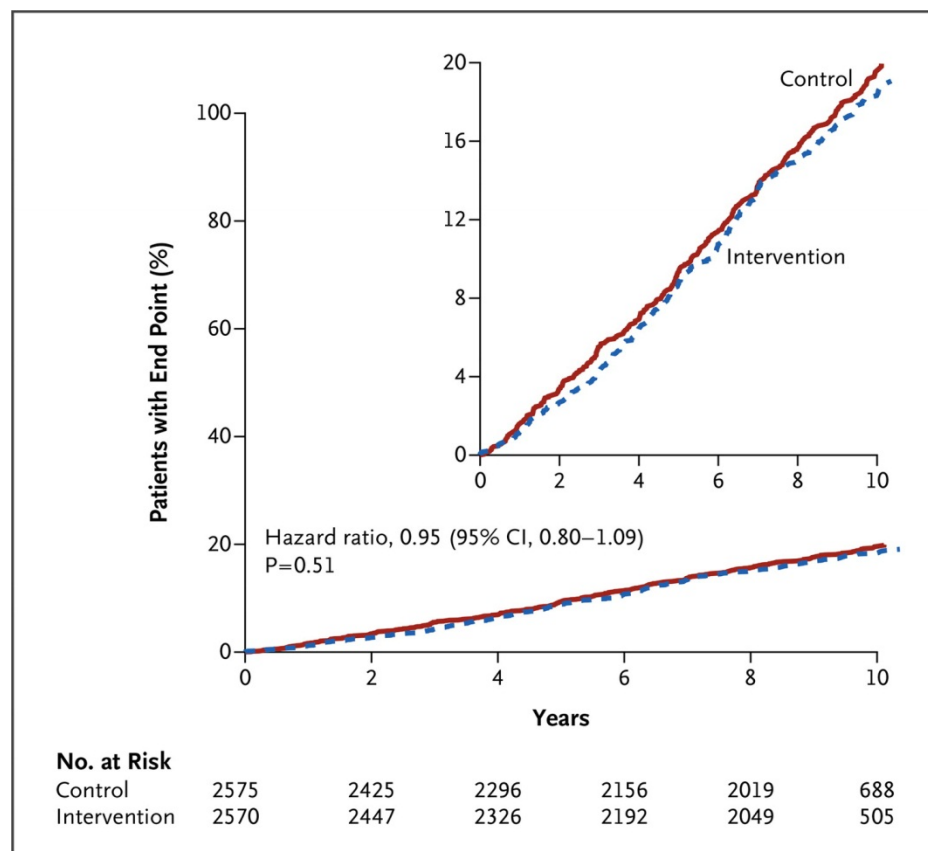
Cardiovascular morbidity and mortality trial

- Overweight and obese adults with type 2 diabetes (N=5145)
- Treatments (1:1 randomization)
 - Intensive lifestyle intervention (intervention group)
 - Reduced calorie diet, meal replacements, increased physical activity, group and individual counseling
 - Diabetes support and education intervention (control group)
 - Group sessions 1-3x/yr focused on diet, exercise, and social support
- Primary endpoint: first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalization for angina
- Median treatment duration: 9.6 years
- Stopped early for futility

Look AHEAD (Action for Health in Diabetes)

Cardiovascular morbidity and mortality trial

Cumulative Hazard Curves for the Primary Composite End Point



- Average weight loss (intervention – control) over 10 years: -4% (95% CI -5, -3); end of trial: -2.5%
- Average change in HbA1c (intervention – control): -0.22 percentage points (95% CI -0.28, -0.16)
- Intervention group had greater improvements in all other CV risk factors, except for LDL-C
- The use of antihypertensive medications, statins, and insulin was lower in the intervention group than in the control group

The Look AHEAD Research Group. N Engl J Med 2013;369:145-154

Cardiovascular Safety and Victoza

- 2008 FDA Guidance: Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes
 - MACE HR upper-bound 95% CI < 1.8 pre-approval*
 - MACE HR upper-bound 95% CI < 1.3 post-approval*
- Clinical development program completed before FDA guidance for CV risk assessment for antidiabetic drugs issued
 - FDA approval relied on meta-analysis of MedDRA preferred terms for CV AEs
 - CV outcomes trial post-marketing requirement (PMR)
- Warnings and Precautions: “There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza or any other antidiabetic drug.”
- Adverse Reactions: “Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established.”

* With a reassuring point estimate

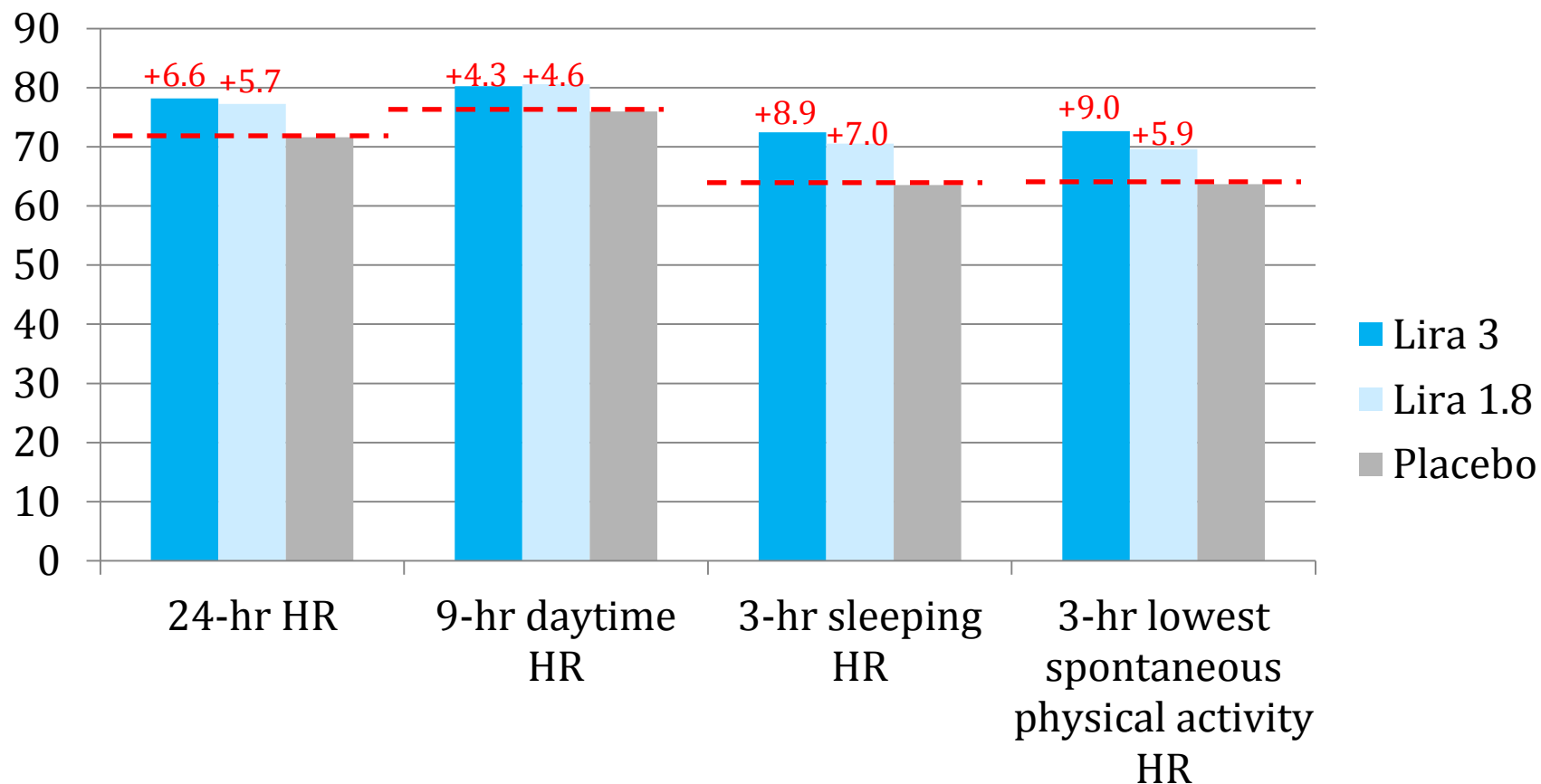
Heart Rate

Weight Management Program

- 24-hr monitoring in Phase 1 clinical pharmacology trial
- Continuous monitoring with polysomnography in Trial 3970
- Routine resting HR

Liraglutide is Associated with Increases in 24-hour Heart Rate

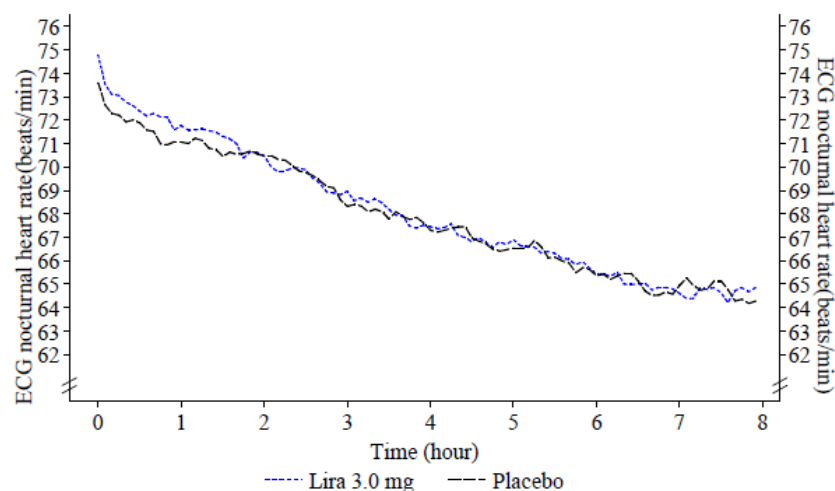
Clinical Pharmacology Trial 3630



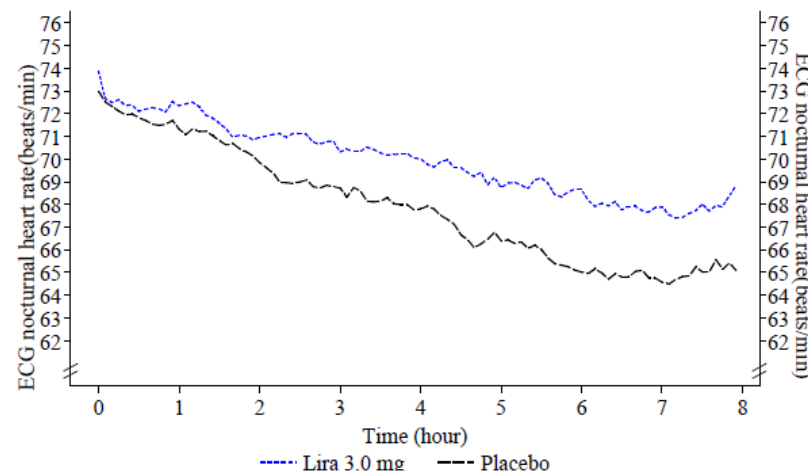
Results shown in beats per minute (bpm)

Liraglutide Attenuates Decrease in Nocturnal HR

Trial 3970, Polysomnography



Screening



Week 32

Figures: 3970 clinical trial report

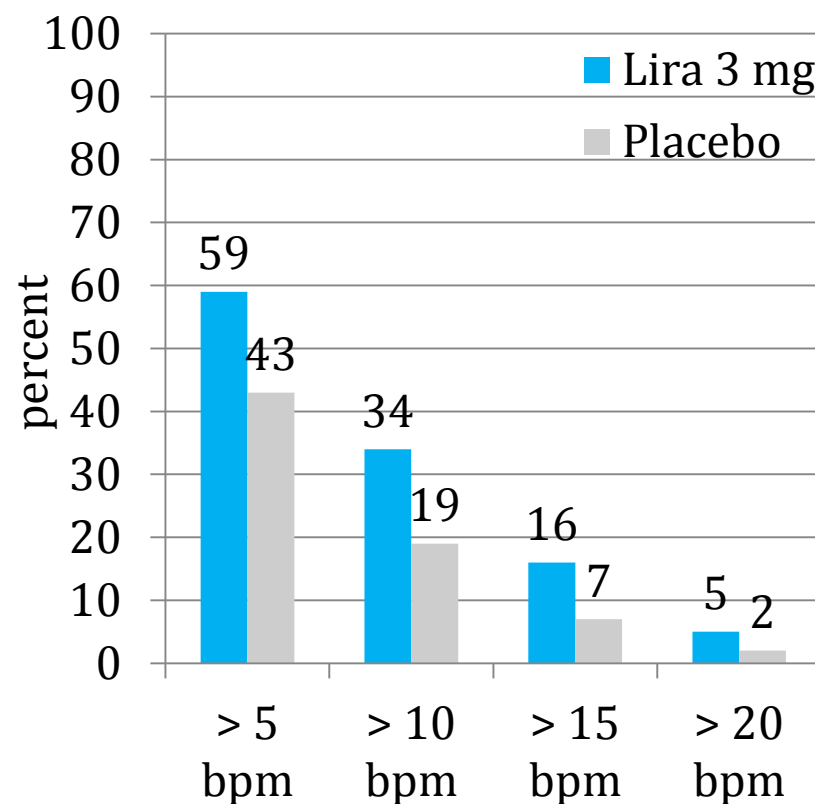
Liraglutide is Associated with Resting HR Increase

Weight Management Pool

Mean HR Increases, bpm Phase 3 56-Week Trials

Trial	Lira 3 mg	Placebo	Treatment Difference
1839	+2.55	+0.10	+2.45 (1.88, 3.02)
1922 T2DM	+1.95	-1.46	+3.40 (1.98, 4.83)
1923	+3.47	+2.49	+0.97 (-0.50, 2.45)

HR Categorical Increases 2 Consecutive Visits



Adjudicated MACE and Heart Failure

- Major Adverse Cardiovascular Events (MACE): CV deaths, non-fatal myocardial infarction, non-fatal stroke
- CV risk margin to rule out was not pre-specified
- On-treatment analysis (weight management pool)
 - 8 events in 3972 liraglutide-treated patients vs. 9 events in 2036 comparator-treated patients
 - HR 0.4 (95% CI 0.15, 1.05)
- Other MACE analyses consistent with primary analysis
- One treatment-emergent case of adjudicated heart failure ('cardiomyopathy') in a patient treated with liraglutide 3 mg with a history of peripartum cardiomyopathy

Deaths

Weight Management Pool

Patient-Trial	Age / Sex / BMI	Days exp	Medical history	Description / Adjudication
D1-1839 Lira 3	50 y / M / 40.5	235	Coronary disease, hypertensive cardiomyopathy	Suddenly collapsed on the street CV Death
D2-1839ext Lira 3	65 y / M / 33.6	578	Coronary artery disease, multiple stent replacements, sleep apnea	Suddenly collapsed at home (ventricular fibrillation) CV Death
D3-1922 Lira 1.8	53 y / M / 52.6	391 (44 d off-drug in follow-up period)	T2DM, cardiovascular disease, cardiomegaly, hypoventilation syndrome, alcohol abuse	Saddle pulmonary embolism and thromboembolic cerebrovascular stroke CV Death
D4-1923 Placebo	58 y / M / 28.3	136	Hypertension, hyperlipidemia, alcohol abuse, smoker	Fatal heart failure; limited info CV Death
D5-1839 Placebo	51 y / M / 29.7	114	Hypertension, hyperlipidemia, pulmonary fibrosis	Worsening pulmonary fibrosis; limited info CV Death
D6-1839 Placebo	59 y / M / 57.6	111	Sleep apnea	Went to dr complaining of chest pain & shortness of breath; dev. asystole; CXR: lung white-out Not CV Death

Cardiovascular Safety, General Comments

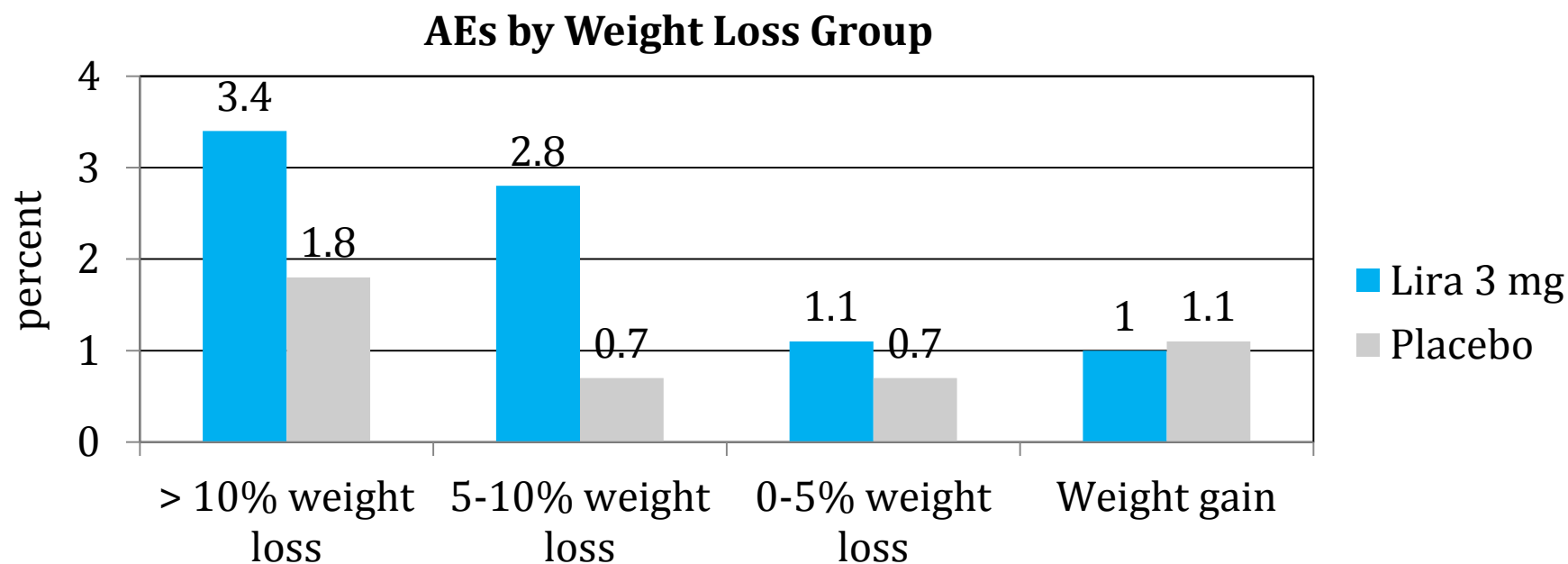
- No clear dose relationship for HR increase
- In setting of mean BP decreases, clinical relevance of increased HR unclear
- Too few MACE to draw conclusions regarding CV safety
- CV outcomes trial ongoing (Victoza 1.8 mg)

Gallbladder and Pancreatitis Adverse Events

Gallbladder AEs

Weight Management Pool

- 'Acute gallstone disease' 2.3% liraglutide 3 mg vs. 0.9% placebo
- Majority of events were 'cholelithiasis' (1.5% vs. 0.5%) and 'cholecystitis acute' (0.4% vs. 0.1%)



Adjudicated Acute Pancreatitis Weight Management Pool

	Lira 3 mg	Placebo
Main periods	N=3291	N=1843
EAC-confirmed events	7 (0.21%)	1 (0.05%)
Ongoing 1839 extension	N=1087	N=497
EAC-confirmed events	2 (0.18%)	0

- 1 patient treated with **lira 3 mg** in trial 1807 (no adjudication) had an SAE of acute pancreatitis
- 3 additional patients treated with **lira 3 mg** had adjudicated pancreatitis events 12-124 days after last drug date

Pancreatitis AEs

Liraglutide-Treated Patients

Patient-Trial	Age / Sex / BMI	Days exp	Relevant details
P1-1839 Lira 3	52 y / M / 62.9	31	Co-reporting of hepatitis 197 kg at baseline, lost 6.4% of body weight in 4 weeks
P2-1839 Lira 3	51 y / M / 32.7	29	No weight loss
P3-1839 Lira 3	58 y / M / 34.7	43	113 kg at baseline, lost 6.6% of body weight in 8 weeks
P4-1839 Lira 3	32 y / F / 38.9	24	Current smoker Ultrasound normal 108 kg at baseline, lost 3.3% of body weight in 2 weeks

Pancreatitis AEs

Liraglutide-Treated Patients

Patient-Trial	Age / Sex / BMI	Days exp	Relevant details
P5-1839 Lira 3	40 y / F / 41.7	283	Cholelithiasis reported at time of event. History of alcohol abuse, current smoker. Lost 19.1% of body weight in 40 weeks
P6-1839 Lira 3	51 y / F / 48.6	277	Previous smoker. Complaint of intermittent abdominal pain; CT day 204 normal.
P7-1839 Lira 3	40 y / M / 54.0	330	174 kg at baseline, wt loss < 3% during trial
P8-1807 Lira 3	42 y / F / 34.2	299	Co-reported with cholelithiasis
P9-1839ext Lira 3	62 y / F / 38.7	410	Positive dechallenge and rechallenge (GI symptoms and increased lipase); normal pancreas on CT
P10-1839ext Lira 3	48 y / F / 45.1	626	Current smoker. Presented with abdominal pain; pancreatitis confirmed by CT; no gallstones

Gallstones and Pancreatitis, Comments

- Liraglutide was associated with increases in the incidence of acute gallstone disease and acute pancreatitis in the weight management trials
- Liraglutide may increase gallstone formation by a weight loss-dependent or independent mechanism, or a combination of both
- Only 2 of 10 liraglutide-treated patients reported to have gallstone pancreatitis, however additional patients may have had rapid or large weight loss that could be consistent with gallstone formation
- At this time, there is not enough information to determine the mechanism underlying the association between liraglutide and pancreatitis

Psychiatric Safety

Regulatory History

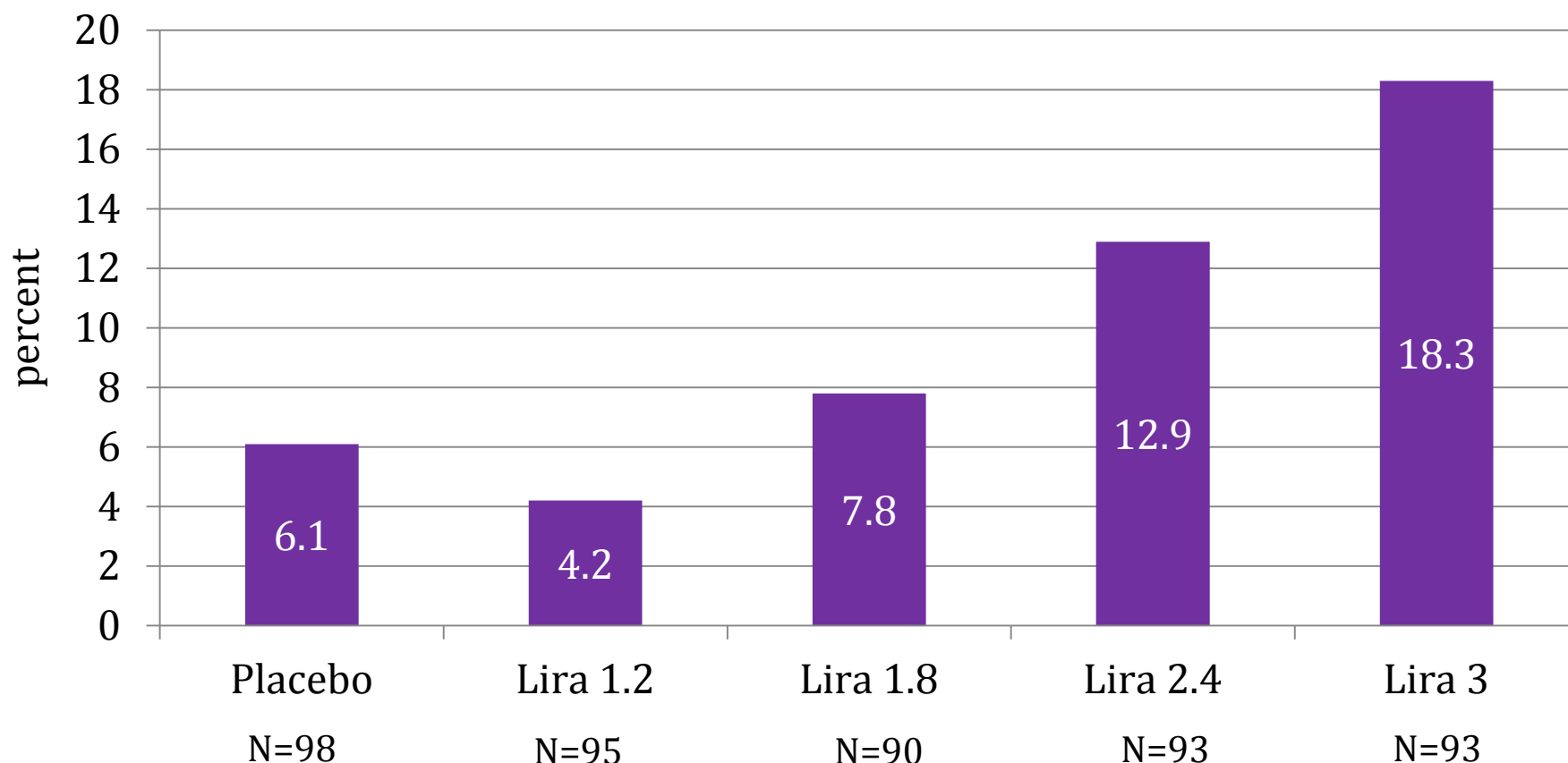
Rimonabant and Neuropsychiatric AEs

- 2007 EMDAC meeting
 - Depression, suicidality, and seizure AEs discussed
 - Trials had high drop-out rates
 - More long-term data needed
 - Vote: 0 yes, 14 no
- Rimonabant never approved in U.S. and removed from European market in 2008
- Centrally-acting weight management drug development now incorporates standard depression and suicidality questionnaires in Phase 2 and 3 clinical trials

Psychiatric Disorders by Dose

Trial 1807

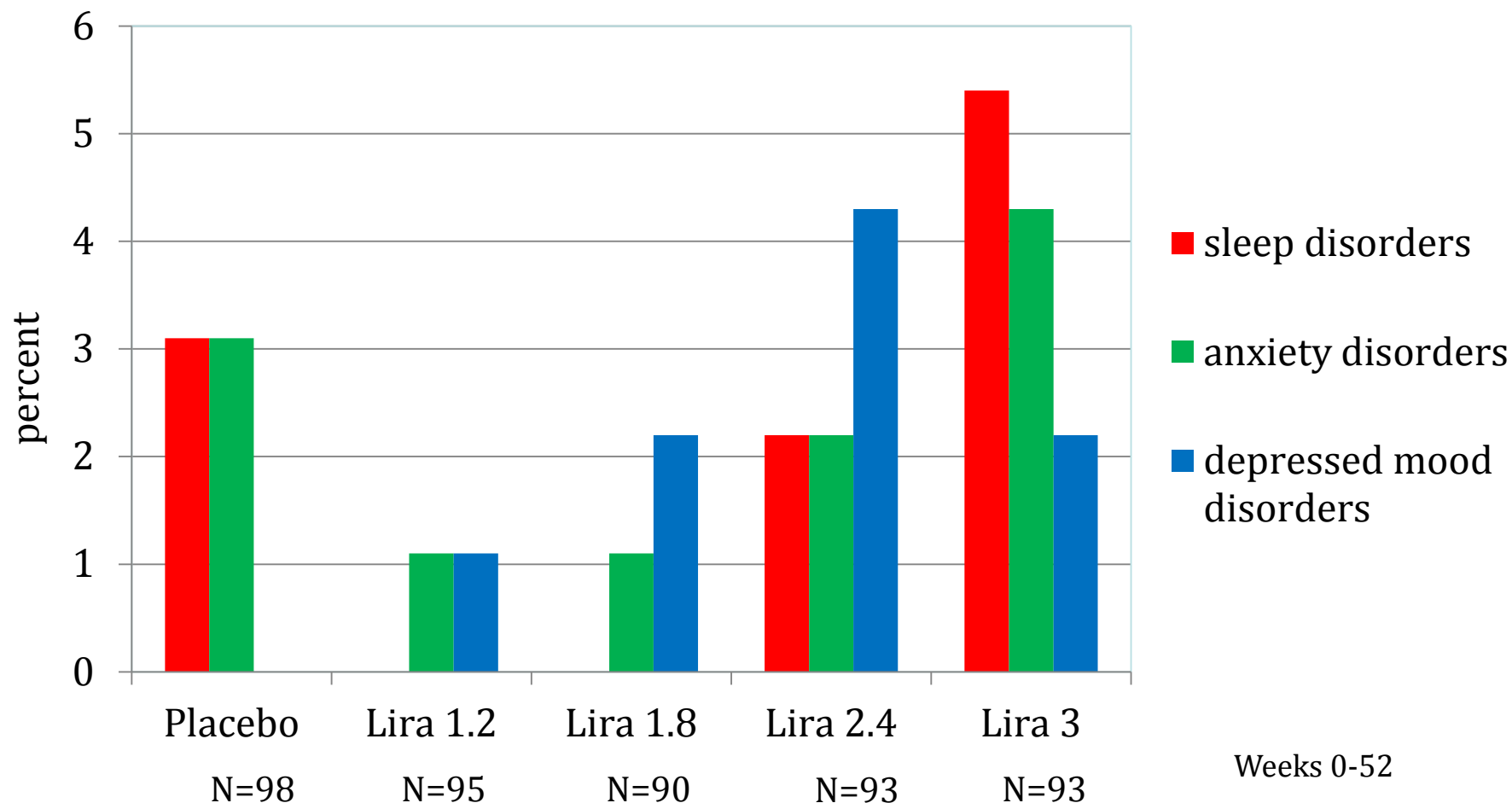
Psychiatric Disorder Standard MedDRA Query



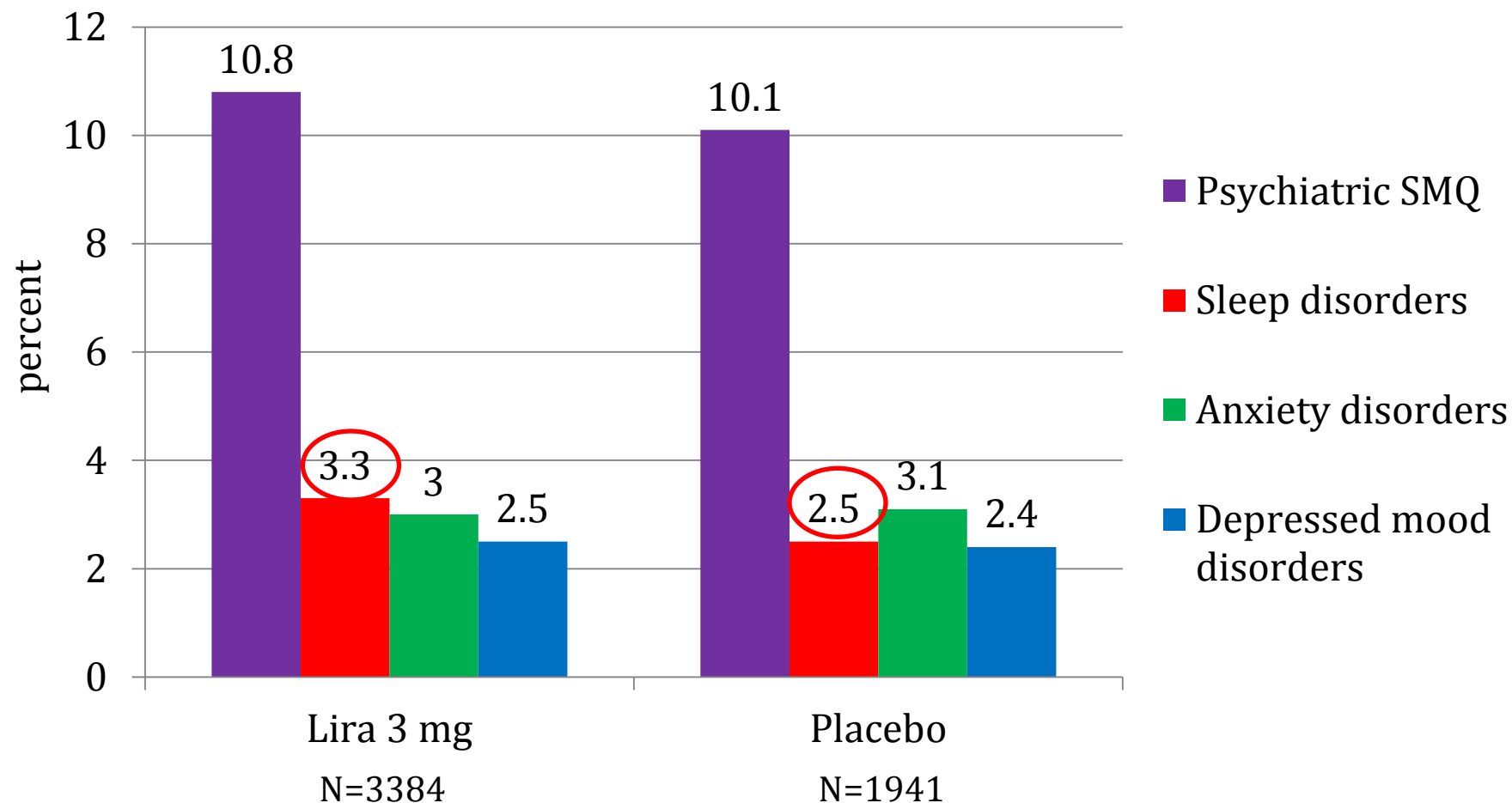
Weeks 0-52

Psychiatric Disorders by Dose

Trial 1807



Psychiatric Disorders Weight Management Pool



Psychiatric Questionnaires

- PHQ-9: 9-item depression subscale of primary care mental health questionnaire
- C-SSRS: standardized assessment to quantify the severity of suicidal ideation and behavior
- Neither scale suggested increases in depressed mood or suicidal ideation with liraglutide as compared with placebo

Suicidality

Patient-Trial	Age / Sex	Days exp	SAE?	Psych. history	D/C drug?	Recovered?
S1-1839 Lira 3	28 y / F	210	N	None	Yes	Depressed mood continued off drug
S2-1839 Lira 3	42 y / F	16	N	None	No	Yes
S3-1839 Lira 3	41 y / F	327	N	Situational depression	No	Yes Depression and anxiety continued
S4-1839 Lira 3	42 y / F	113	Y Suicide attempt	Depression	Yes – 1 yr later	Yes –after d/c Major depression continued
S5-3970 Lira 3	36 y / F	203	Y	Anxiety & depression	No	No
S6-1839ext Lira 3	49 y / M	697	Y Seen in ER, not hospitalized	None	No	Yes

Neoplasms

Neoplasms, General Comments

- Sponsor undertook an independent adjudication process in the 4 Phase 3 weight management trials (1923, 1839, 1922, 3970)
- Neoplasms in diabetes trials and Phase 2 trial 1807 were not adjudicated and rely on AE terms
 - Poor specificity (preferred term “thyroid neoplasm” mostly thyroid nodules)
 - Pooling allows for a larger denominator (might detect events of low incidence)
 - Limitations include different patient populations, doses, and comparators
- Potential detection biases could result from increased weight loss, more GI complaints in liraglutide arm

Neoplasms

Weight Management Pool

- Malignant breast cancer (including *in situ*) imbalance noted
 - No pattern in the timing of events, association with baseline BMI, risk factors
 - Not aware of any data supportive of biological plausibility
- Medullary thyroid cancer (MTC) and cancer of the exocrine pancreas were not observed in liraglutide-treated patients in the weight management clinical trials
 - All thyroid neoplasms in liraglutide-treated patients were of papillary or follicular origin
 - Single case of C-cell hyperplasia (co-reported in a patient diagnosed with papillary microcarcinoma) adjudicated to have onset date prior to trial start
 - Single case of MTC was reported in a patient treated with placebo

Adjudicated Thyroid Cancer

Weight Management Trials, Liraglutide-Treated Patients

Patient-Trial	Age / Sex	Days exp	Diagnosis / EAC category	Findings at baseline	Tumor size / other features
T1-1839 Lira 3	27 y / M	211	Papillary thyroid carcinoma Malignant	Thyroid nodule suspected at screening	R - 1.35 cm with extension L - 0.5 cm
T2-1839 Lira 3	40 y / F	180	Papillary thyroid carcinomas (x2) Malignant		1.2 x 1.0 x 1.6 cm on ultrasound
T3-1922 Lira 3	58 y / M	358	Papillary microcarcinoma Pre-malignant	Elevated calcitonin at baseline	1 mm + reactive C-cell hyperplasia in both lobes; RET negative
T4-1923 Lira 3	42 y / F	15	Papillary thyroid carcinomas Malignant	History of nodules, enlarged thyroid at screening	"large" nodule
T5-1922 Lira 3	56 y / F	137 (after w/d)	Papillary microcarcinoma Pre-malignant		0.5 mm, detected during thyroidectomy (thyroid nodule on examination – benign adenoma)
T6-1839ext Lira 3	43 y / F	552	Papillary microcarcinoma Malignant	H/o parathyroidectomy	3 mm - incidentally found during exploratory surgery for increasing PTH
T7-1839 Lira 3	61 y / F	142 (after w/d)	Papillary microcarcinoma Pre-malignant		3 mm - incidentally found during thyroidectomy for multinodular goiter (autoimmune thyroiditis)