

Pulmonary Allergy Drugs  
Advisory Committee Meeting  
Olodaterol Inhalation Spray  
NDA 203108

Theresa M. Michele, MD  
Clinical Team Leader  
Division of Pulmonary, Allergy, and Rheumatology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
January 29, 2013

## Olodaterol (Striverdi Respimat)

- New molecular entity
- Beta<sub>2</sub>-adrenergic agonist
- Other beta<sub>2</sub>-adrenergic agonists
  - Long-acting beta-adrenergic agonist (LABA)
    - Salmeterol
    - Formoterol
    - Indacaterol
  - Short-acting beta-adrenergic agonist (SABA)
    - Albuterol
- Inhalation solution using the Respimat device

# Olodaterol

- Indication
  - Olodaterol is a beta<sub>2</sub>-adrenergic agonist indicated for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
- Dosage and Administration
  - The recommended dose is 5 mcg (two actuations of 2.5 mcg each) once-daily

## Topics for Discussion

- Efficacy data
  - Bronchodilation
  - Exercise Tolerance
- Safety data

## Overview of Development – Key Efficacy Trials

<b>Trial Type</b>	<b>Population</b>	<b>Number of Trials</b>
Dose-ranging	COPD	3
Dose-ranging	Asthma	4
6-week spirometry	COPD	4
48-week spirometry	COPD	4
6-week exercise tolerance	COPD	2

# 48-week Spirometry Trials

<b>Trial Year Completed</b>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Primary Endpoints</b>	<b>Sites</b>
1222.11 2010	R, DB, PC, PG 48-week treatment	625	Olo 5mcg qD Olo 10mcg qD Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 At 12 weeks	Europe, Asia, Australia, New Zealand, US (54 sites)
1222.12 2010	R, DB, PC, PG 48-week treatment	644	Olo 5mcg qD Olo 10mcg qD Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 At 12 weeks	Europe, Asia, US (52 sites)
1222.13 2010	R, DB, DD, PC, PG 48-week treatment	906	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 TDI At 24 weeks	Europe, Asia, Africa (94 sites)
1222.14 2010	R, DB, DD, PC, PG 48-week treatment	937	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 TDI At 24 weeks	Europe, Asia, Africa (103 sites)

Key: N=randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, DD= double-dummy PC=placebo control, PG=parallel group, AC=active control, CO=crossover, TDI=transitional dyspnea index

## 6-week Exercise Tolerance Trials

<b>Trial</b> <i>Year Completed</i>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Pertinent Endpoints</b>	<b>Sites</b>
1222.37 2011	R, DB, PC, CO 6-week treatment	151	Olo 5mcg qD Olo 10mcg qD Placebo	Endurance time Inspiratory capacity	Europe, Canada, Australia (16 sites)
1222.38 2011	R, DB, PC, CO 6-week treatment	157	Olo 5mcg qD Olo 10mcg qD Placebo	Endurance time Inspiratory capacity	Europe, Canada (16 sites)

Key: N=Randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, PC=placebo-control, CO=crossover

## Purpose of Proceedings Before an Advisory Committee (21 CFR 14.5)

- An advisory committee is utilized to conduct public hearing on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner
- The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee





*Thank You!*

Pulmonary Allergy Drugs  
Advisory Committee Meeting  
Olodaterol Inhalation Spray  
NDA 203108

Robert Lim, MD  
Clinical Reviewer  
Division of Pulmonary, Allergy, and Rheumatology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
January 29, 2013

## Objectives

- To discuss the efficacy of olodaterol inhalation spray for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
- To discuss the proposed exercise claims
- To discuss the safety of olodaterol inhalation spray

# Outline

- Overview of the Clinical Program

*Robert Lim, MD*

*Clinical Reviewer, DPARP, CDER, FDA*

- Statistical Review of Efficacy

*Robert Abugov, PhD*

*Statistical Reviewer, DB II, CDER, FDA*

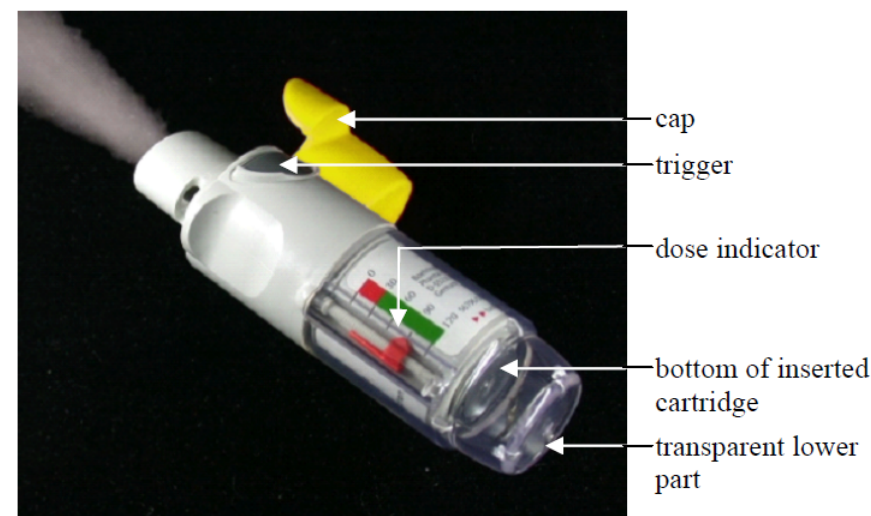
- Clinical Review of Efficacy, Safety, Risk/Benefit

*Robert Lim, MD*

*Clinical Reviewer, DPARP, CDER, FDA*

## Striverdi Respimat (Olodaterol Inhalation Spray)

- New molecular entity
- Long-acting beta-agonist (LABA)
- Administered via the Respimat device
  - Approved for use with Combivent
- 5 µg (2.5 µg /actuation) once daily
- Proposed for the long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema



## Regulatory History

- 2008 End of phase 2 meeting
  - Agreed that 5mcg and 10mcg total daily doses were reasonable to carry forward into phase 3
  - Dose interval had not been established
- 2009 Advice request
  - Presented data in COPD patients to support once daily dosing
  - Recommendation that dose and dose interval be explored in asthmatics
- 2011 Pre-NDA interaction

## Overview of Development – Key Efficacy Trials

<b>Trial Type</b>	<b>Population</b>	<b>Number of Trials</b>
Dose-ranging	COPD	3
Dose-ranging	Asthma	4
6-week spirometry	COPD	4
48-week spirometry	COPD	4
6-week exercise tolerance	COPD	2

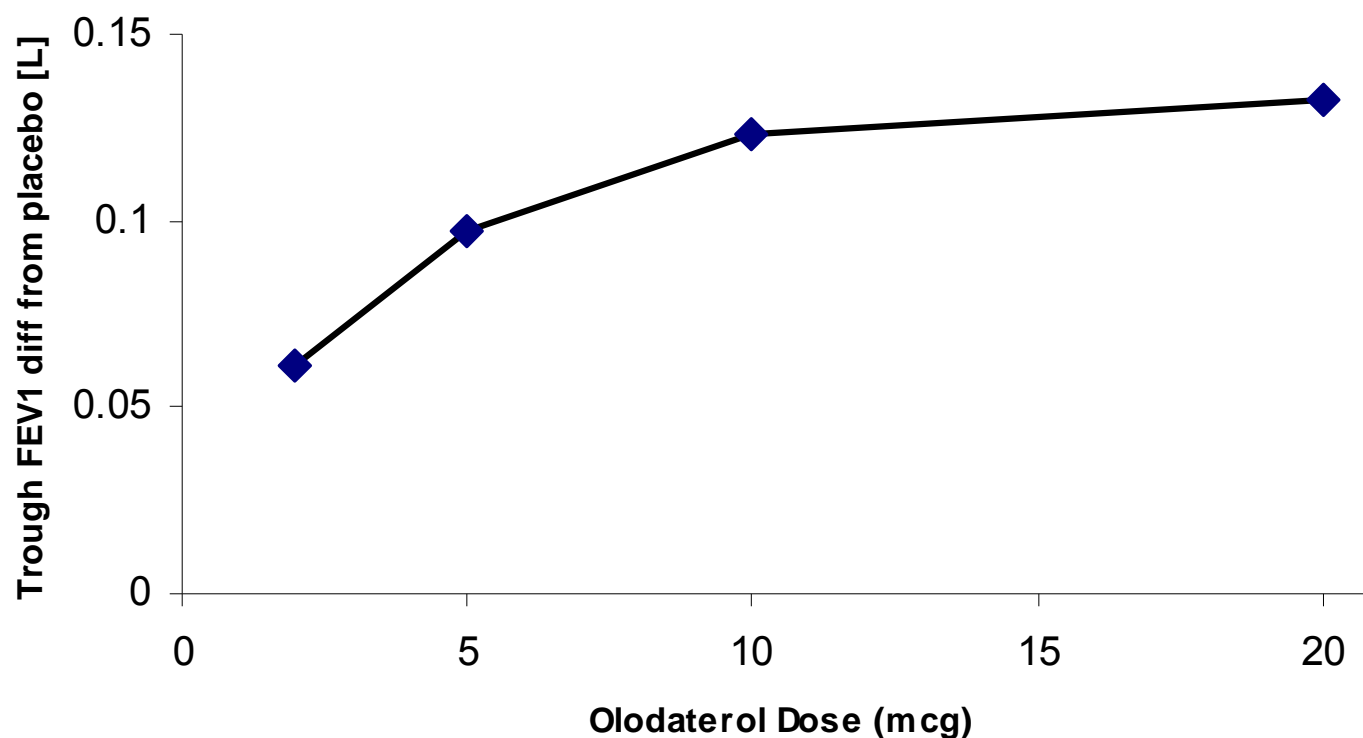
# COPD – Dose-Ranging Trials

<b>Trial Year Completed</b>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Primary Endpoint(s)</b>	<b>Sites</b>
1222.3 2006	R, DB, PC, CO Single-dose	36	Olo 2mcg Olo 5mcg Olo 10mcg Olo 20mcg Placebo	FEV1 24-hour post dose	Netherlands (1 site)
1222.5 2008	R, DB, PC, PG 4-week treatment	405	Olo 2mcg qD Olo 5mcg qD Olo 10mcg qD Olo 20mcg qD Placebo	Trough FEV1	USA, Canada, Europe (24 sites)
1222.26 2009	R, DB, CO 3-week treatment	47	Olo 2mcg BID Olo 5mcg qD Olo 5mcg BID Olo 10mcg qD	FEV1 AUC(0 - 12hrs) FEV1 AUC(12 - 24hrs)	Europe (5 sites)

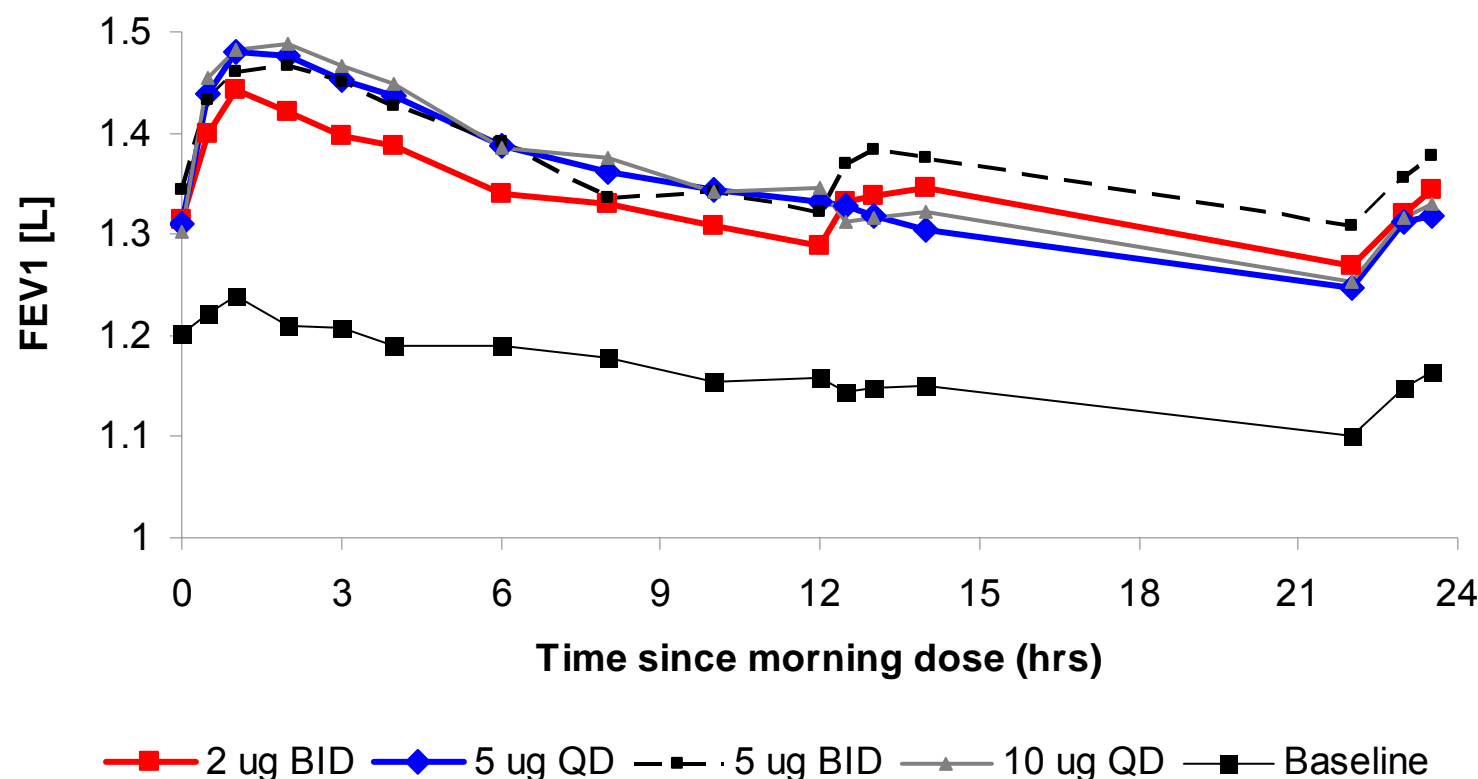
Key: N=randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, PC=placebo control, PG=parallel group, CO=crossover



# COPD Dose-Ranging Trial 1222.5



# COPD Dose-Regimen Trial 1222.26



# Asthma – Dose-Ranging Trials

<b>Trial</b> <i>Year Completed</i>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Endpoint</b>	<b>Sites</b>
1222.4 2006	R, DB, PC, CO Single-dose	31	Olo 2mcg Olo 5mcg Olo 10mcg Olo 20mcg Placebo	Log <sub>2</sub> (PC20 FEV1)	Canada (4 sites)
1222.6 2008	R, DB, PC, PG 4-week treatment	296	Olo 2mcg qD Olo 5mcg qD Olo 10mcg qD Olo 20mcg qD Placebo	Trough FEV1	Canada, Europe, US (4 sites)
1222.27 2011	R, DB, PC, AC, CO, DD 4-week treatment	198	Olo 2mcg qD Olo 5mcg qD Olo 10mcg qD Olo 20mcg qD Foradil BID Placebo	FEV1 AUC(0 - 24hrs)	Europe (27 sites)
1222.29 2011	R, DB, PC, CO 3-week treatment	206	Olo 2.5mcg BID Olo 5mcg qD Olo 10mcg qD Olo 5mcg BID Placebo	FEV1 AUC(0 - 24hrs)	Europe, US (36 sites)

Key: N=randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, PC=placebo control, PG=parallel group, CO=crossover, DD= double-dummy, AC=active control

## 6-week Spirometry Trials

<b>Trial Year Completed</b>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Primary Endpoints</b>	<b>Sites</b>
1222.24 2010	R, DB, DD, PC, AC, CO 6-week treatment	99	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 12hrs) FEV1 AUC (12 - 24hrs)	US (11 sites)
1222.25 2010	R, DB, DD, PC, AC, CO 6-week treatment	100	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 12hrs) FEV1 AUC (12 - 24hrs)	US (13 sites)
1222.39 2010	R, DB, DD, PC, AC, CO 6-week treatment	108	Olo 5mcg qD Olo 10mcg qD Tiotropium Placebo	FEV1 AUC (0 - 12hrs) FEV1 AUC (12 - 24hrs)	Europe (15 sites)
1222.40 2011	R, DB, DD, PC, AC, CO 6-week treatment	122	Olo 5mcg qD Olo 10mcg qD Tiotropium Placebo	FEV1 AUC (0 - 2hrs) FEV1 AUC (12 - 24hrs)	Europe (12 sites)

Key: N=randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, DD= double-dummy PC=placebo control, AC=active control, CO=crossover

## 48-week Spirometry Trials

<b>Trial Year Completed</b>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Primary Endpoints</b>	<b>Sites</b>
1222.11 2010	R, DB, PC, PG 48-week treatment	625	Olo 5mcg qD Olo 10mcg qD Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 At 12 weeks	Europe, Asia, Australia, New Zealand, US (54 sites)
1222.12 2010	R, DB, PC, PG 48-week treatment	644	Olo 5mcg qD Olo 10mcg qD Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 At 12 weeks	Europe, Asia, US (52 sites)
1222.13 2010	R, DB, DD, PC, PG 48-week treatment	906	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 TDI At 24 weeks	Europe, Asia, Africa (94 sites)
1222.14 2010	R, DB, DD, PC, PG 48-week treatment	937	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 TDI At 24 weeks	Europe, Asia, Africa (103 sites)

Key: N=randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, DD= double-dummy PC=placebo control, PG=parallel group, AC=active control, CO=crossover, TDI=transitional dyspnea index

# Comparison of 48-week Spirometry Trials

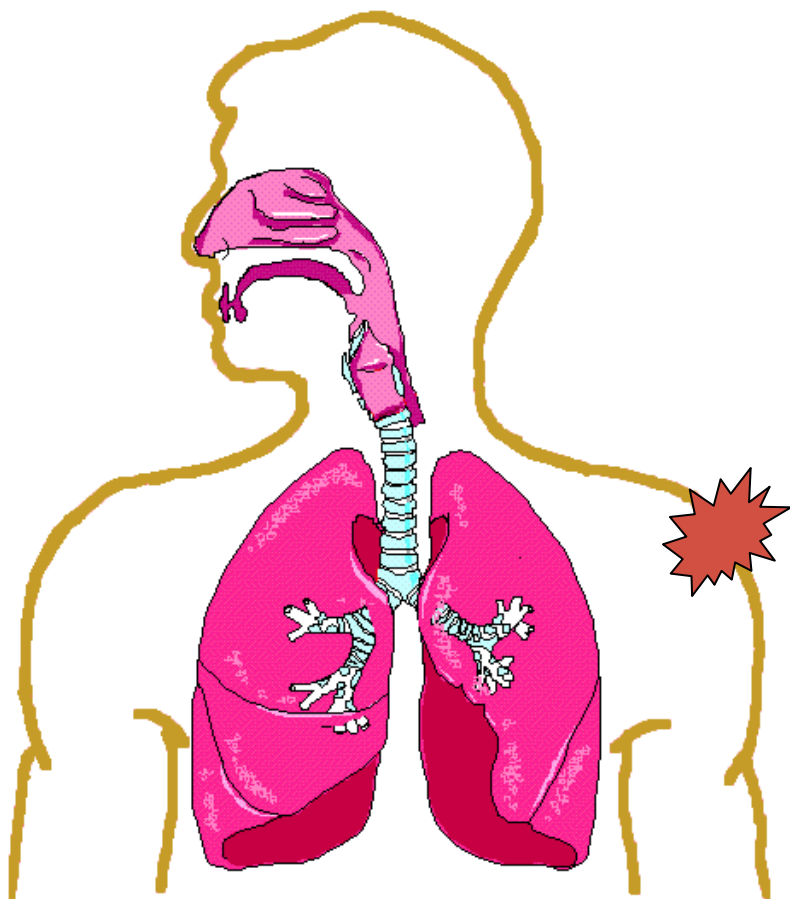
- Key Similarities
  - Allowed usual COPD care
  - Spirometric co-primary endpoints
    - Trough FEV1
    - FEV1 AUC (0-3hr)
- Key Differences
  - Timing of co-primary endpoint assessment
  - Transitional Dyspnea Index
  - Statistical analysis

## 6- week Exercise Tolerance Trials

<b>Trial Year Completed</b>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Pertinent Endpoints</b>	<b>Sites</b>
1222.37 2011	R, DB, PC, CO 6-week treatment	151	Olo 5mcg qD Olo 10mcg qD Placebo	Endurance time Inspiratory capacity	Europe, Canada, Australia (16 sites)
1222.38 2011	R, DB, PC, CO 6-week treatment	157	Olo 5mcg qD Olo 10mcg qD Placebo	Endurance time Inspiratory capacity	Europe, Canada (16 sites)

Key: N=Randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, PC=placebo-control, CO=crossover

## Division of Pulmonary, Allergy and Rheumatology Products





Pulmonary Allergy Drugs  
Advisory Committee Meeting  
Olodaterol Inhalation Spray  
NDA 203108

Robert Abugov, Ph.D.  
Statistical Reviewer, Office of Biostatistics  
Office of Translational Sciences  
Center for Drug Evaluation and Research  
Food and Drug Administration  
January 29, 2013

# Outline

- Design, Issues, Results, and Interim Summaries for
  - 48 Week Spirometry Trials
  - Six Week Spirometry Trials
  - Six Week Exercise Tolerance Trials
- Subgroup Analyses
- Summary

# 48 Week Spirometry Trials

- Design and Analysis
- Issues
- Results
  - Primary Endpoints (Week 12)
    - $\Delta$ Trough FEV<sub>1</sub>
    - $\Delta$  FEV1 AUC<sub>0-3hr</sub>
  - Secondary Endpoints
    - $\Delta$  FEV<sub>1</sub> AUC<sub>0-12hr</sub> (Week 12)
    - Incidence Moderate Exacerbations
    - SGRQ
- Interim Summary

# Statistical Analyses: 48 Week Spirometry

Study	Endpoints	Contrasts	Analysis
1222.11 1222.12 ~47% USA Parallel arm	Primary (Week 12): $\Delta FEV_1$ AUC <sub>0-3hr</sub> $\Delta$ Trough FEV <sub>1</sub>  Secondary: $\Delta FEV_1$ AUC <sub>0-12hr</sub> Week 12 Moderate exacerbations	Olo 10 v P Olo 5 v P	MMRM (Mixed model repeated measures )  Trt, day, tio, baseline, trt*day, baseline*day, tio*trt, tio*day, trt*tio*day
1222.13 1222.14 No USA Parallel arm	Primary (Week 24): $\Delta FEV_1$ AUC <sub>0-3hr</sub> $\Delta$ Trough FEV <sub>1</sub> Mahler TDI focal score  Secondary: SGRQ Week 24 Moderate exacerbations	Olo 10 v P Olo 5 v P	MMRM  Trt, day, tio, baseline trt*day, baseline*day

# Control of Type I Error: Analysis Hierarchy

- Primary Endpoints
  1.  $\Delta \text{FEV}_1 \text{ AUC}_{0-3h}$  olodaterol 10 mcg
  2.  $\Delta \text{Trough FEV}_1$  olodaterol 10 mcg
  3.  $\Delta \text{FEV}_1 \text{ AUC}_{0-3h}$  olodaterol 5 mcg
  4.  $\Delta \text{Trough FEV}_1$  olodaterol 5 mcg

# Statistical Analyses: 48 Week Spirometry

Study	Endpoints	Contrasts	Analysis
1222.11 1222.12 ~47% USA Parallel arm	Primary (Week 12): $\Delta\text{FEV}_1$ $\text{AUC}_{0-3\text{hr}}$ $\Delta\text{Trough FEV}_1$  Secondary: $\Delta\text{FEV}_1$ $\text{AUC}_{0-12\text{hr}}$ Week 12 Moderate exacerbations	Olo 10 v P Olo 5 v P	Mixed model repeated measures  Trt, day, tio, baseline, trt*day, baseline*day, tio*trt, tio*day, trt*tio*day
1222.13 1222.14 No USA Parallel arm	Primary (Week 24): $\Delta\text{FEV}_1$ $\text{AUC}_{0-3\text{hr}}$ $\Delta\text{Trough FEV}_1$ Mahler TDI focal score  Secondary: SGRQ Week 24 Moderate exacerbations	Olo 10 v P Olo 5 v P	Mixed model repeated measures  Trt, day, tio, baseline trt*day, baseline*day

# Issues

- Studies 11 and 12
  - Post-hoc removal of tiotropium by treatment interaction
    - Inappropriately increases estimate of olodaterol's effects
      - No control of Type I error
      - No evidence that tiotropium reduces effect of olodaterol

# 48 Week Spirometry Trials

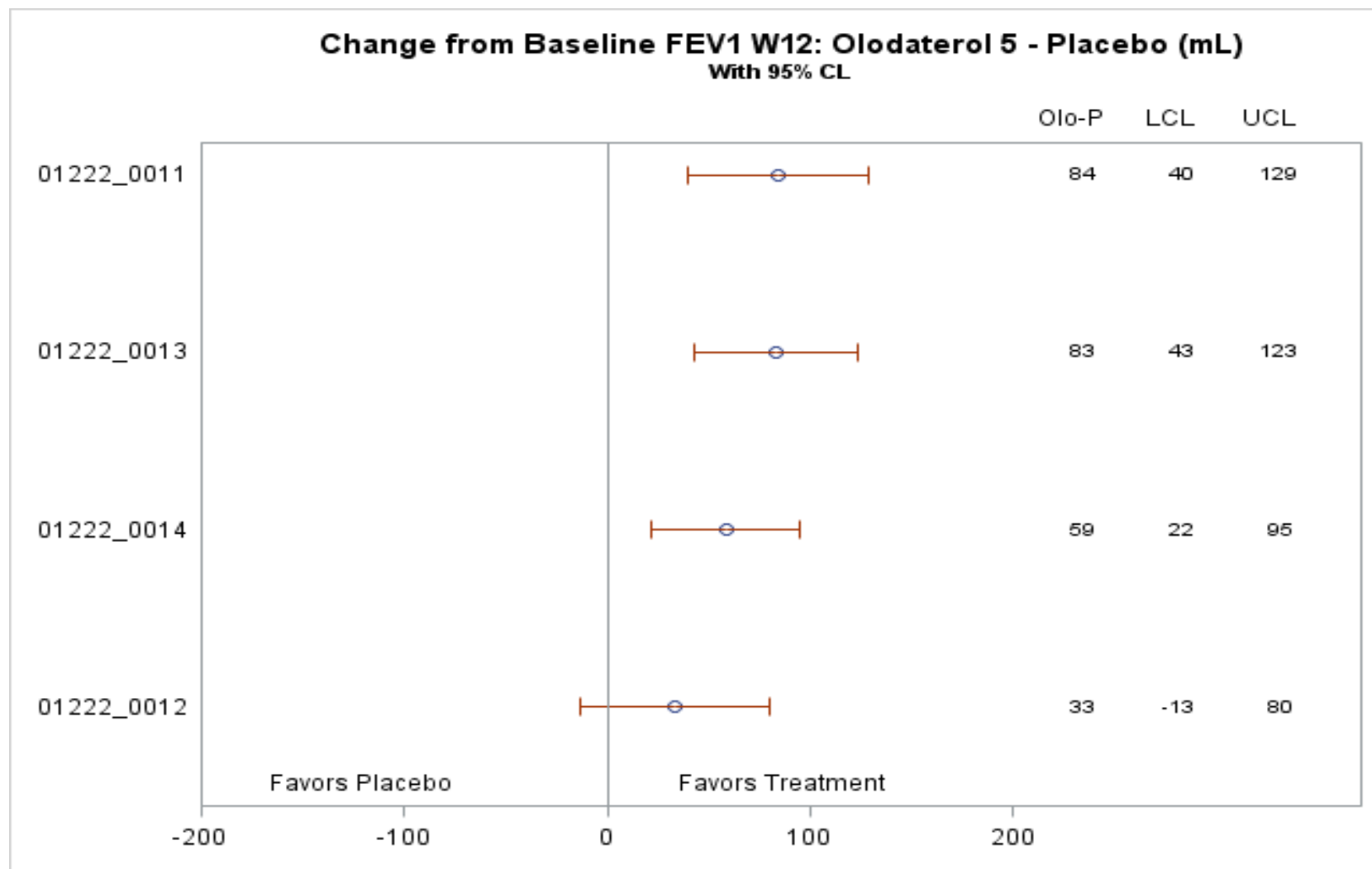
- Design and Analysis
- Issues
- **Results**
  - Primary Endpoints (Week 12)
    - $\Delta$ Trough  $FEV_1$
    - $\Delta FEV_1 AUC_{0-3hr}$
  - Secondary Endpoints
    - $\Delta FEV_1 AUC_{0-12hr}$  (Week 12)
    - Incidence Moderate Exacerbations
    - SGRQ
- Interim Summary



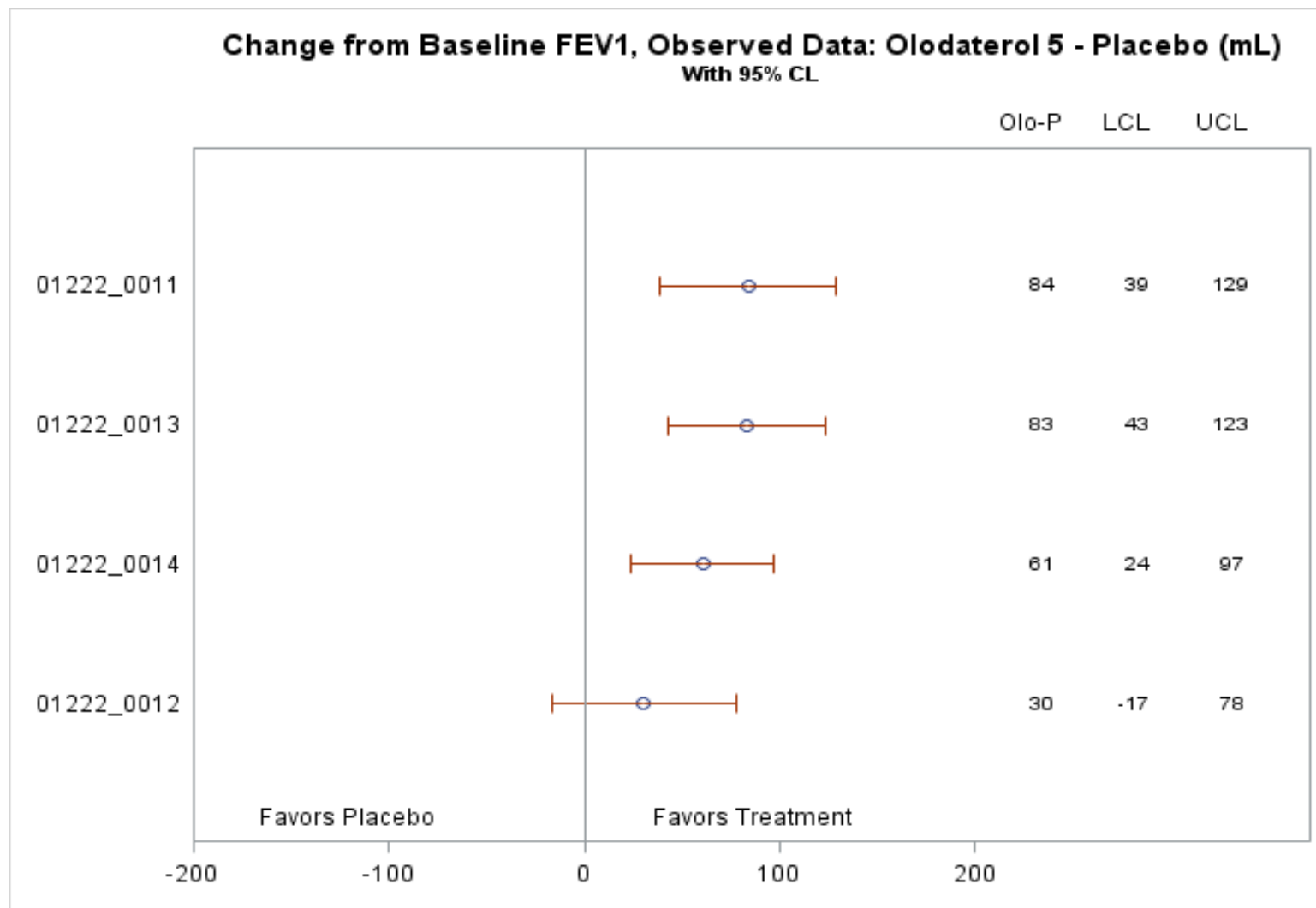
# Concomitant Meds

Concomitant Medication	Study (N)			
	11 (620)	12 (637)	13 (885)	14 (928)
Systemic steroid	27%	24%	24%	25%
Oral steroid	24%	21%	22%	23%
Inhaled steroid	50%	46%	51%	57%
Mucolytic	12%	8%	15%	19%
Xanthine	22%	17%	19%	22%
Antileucotriene	5%	5%	1%	3%
Short-acting anticholinergic	27%	25%	31%	27%
LABA	2%	3%	2%	1%
Long-acting anticholinergic	26%	22%	26%	25%
No concomitant medication	24%	29%	19%	19%

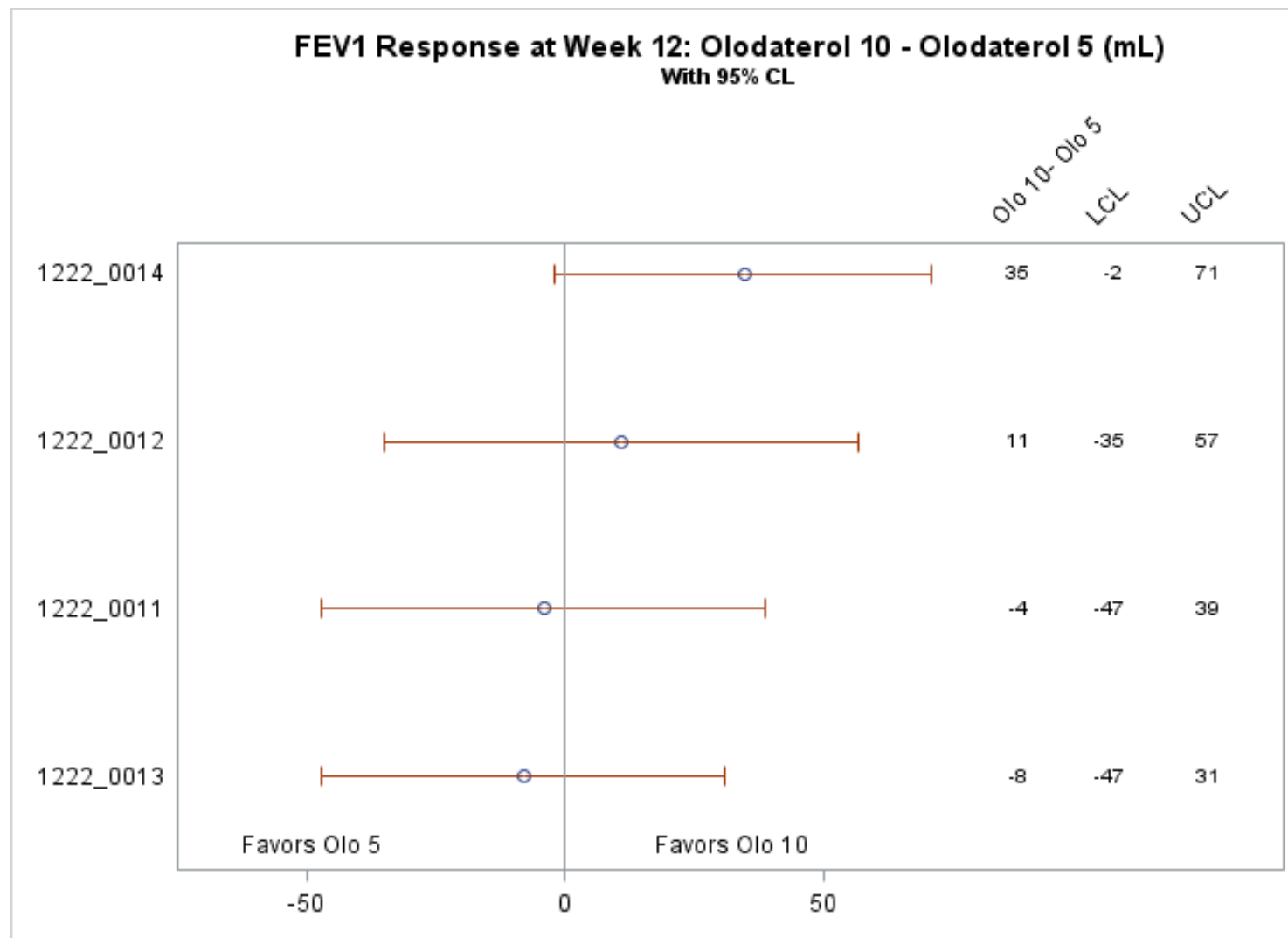
# Primary Endpoint: Week 12 Trough FEV<sub>1</sub> Response (Olodaterol 5 - Placebo)



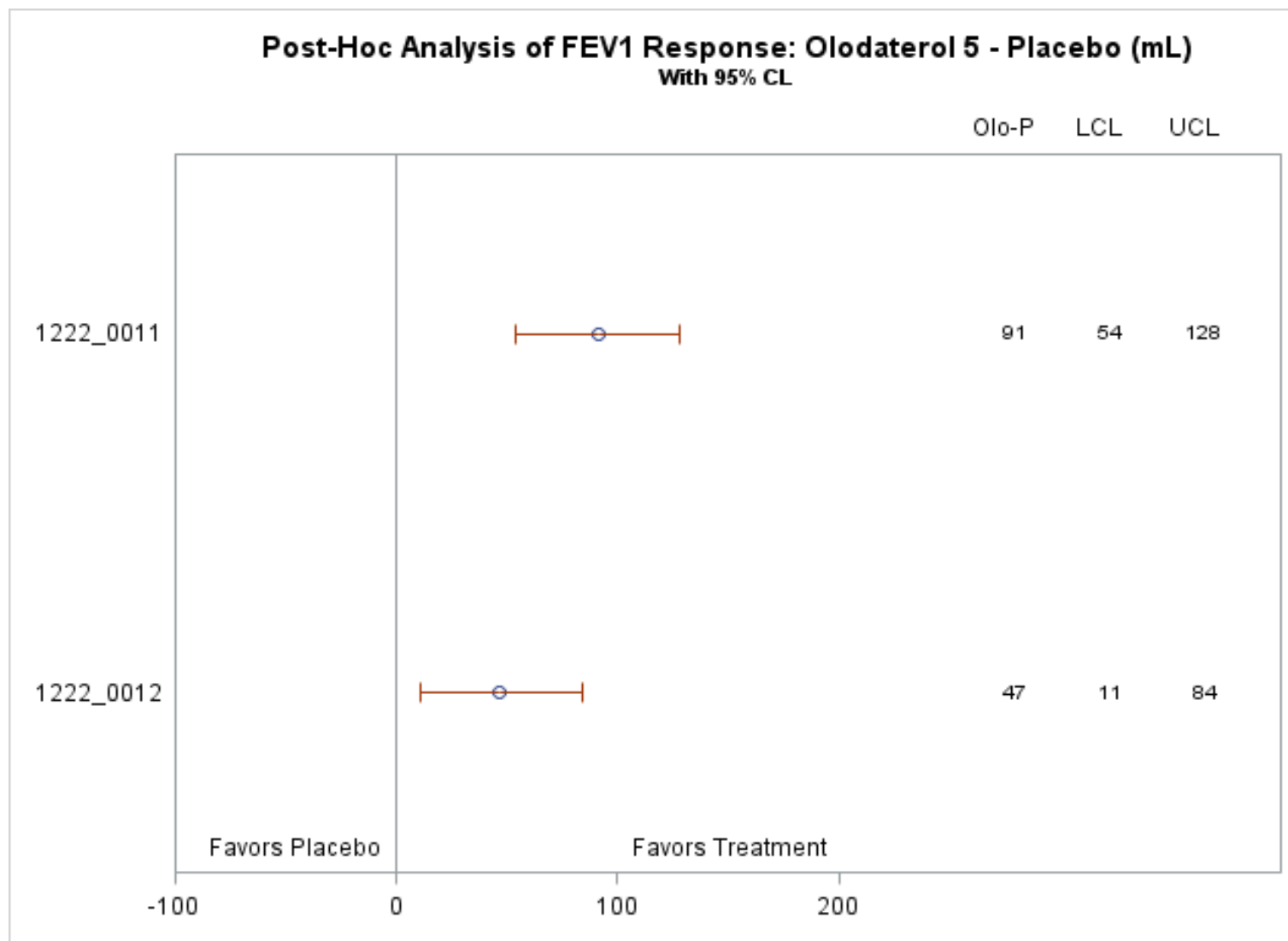
# Primary Endpoint Sensitivity Analysis: Week 12 Trough FEV<sub>1</sub> Response Observed Data Only



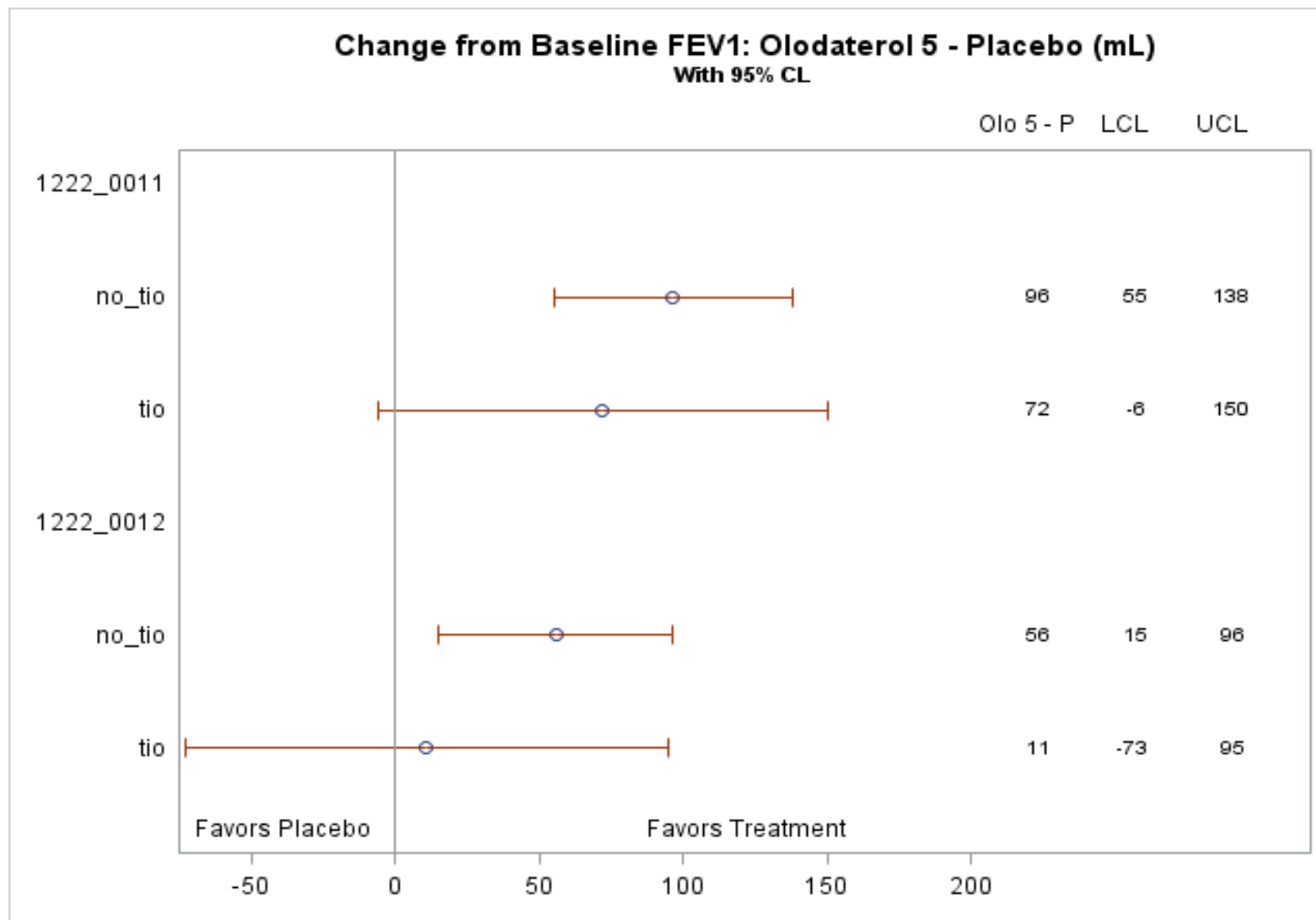
# Primary Endpoint: Week 12 Trough FEV<sub>1</sub> (Olo 10 vs Olo 5)



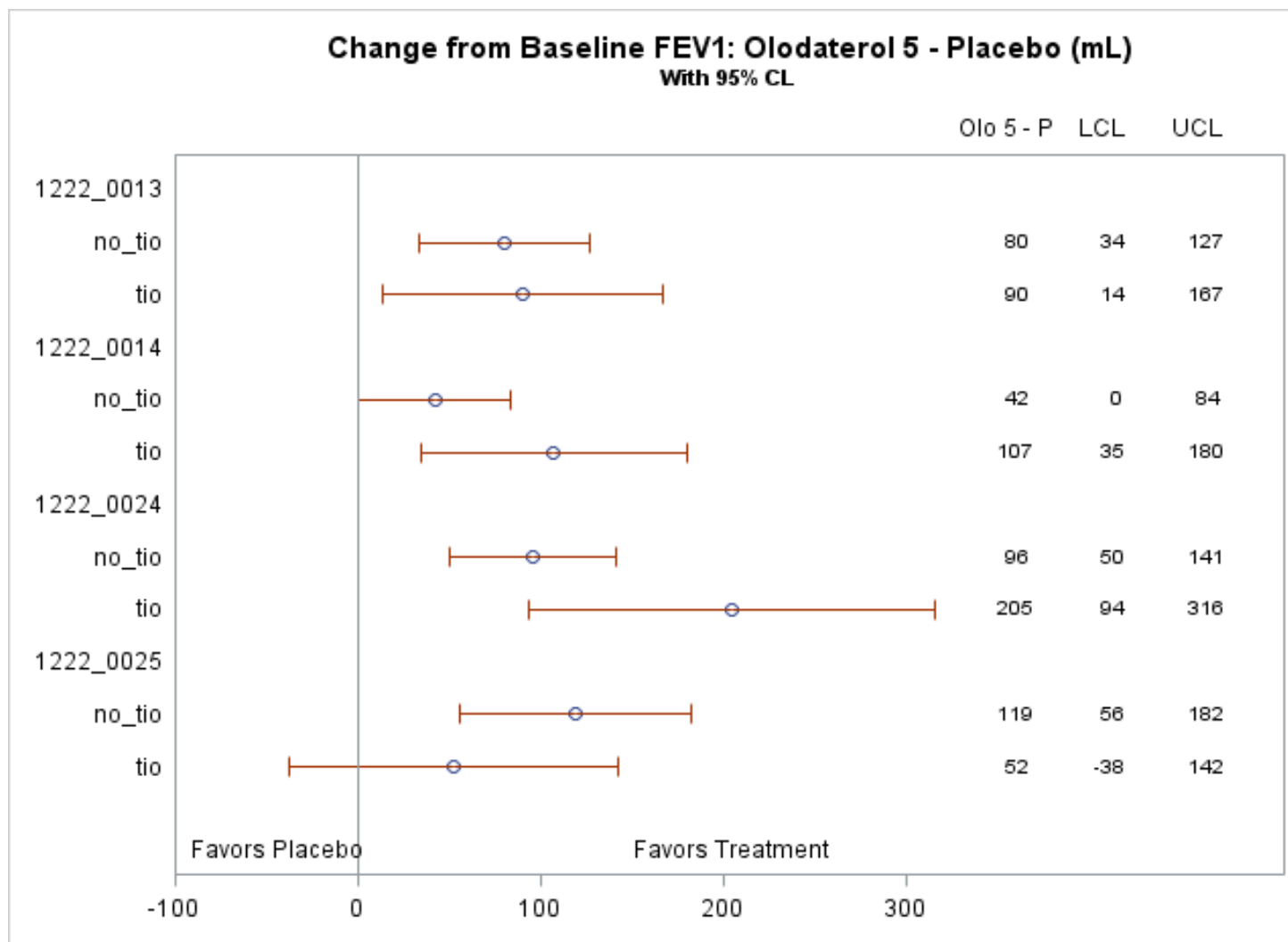
# Week 12 Trough FEV<sub>1</sub> Response: Post-hoc Analysis



# Trough FEV<sub>1</sub> Response Stratified by Tiotropium Use (Post-hoc Studies 11 and 12)



# Trough FEV<sub>1</sub> Response Stratified by Tiotropium Use (Studies 13, 14, 24, and 25)



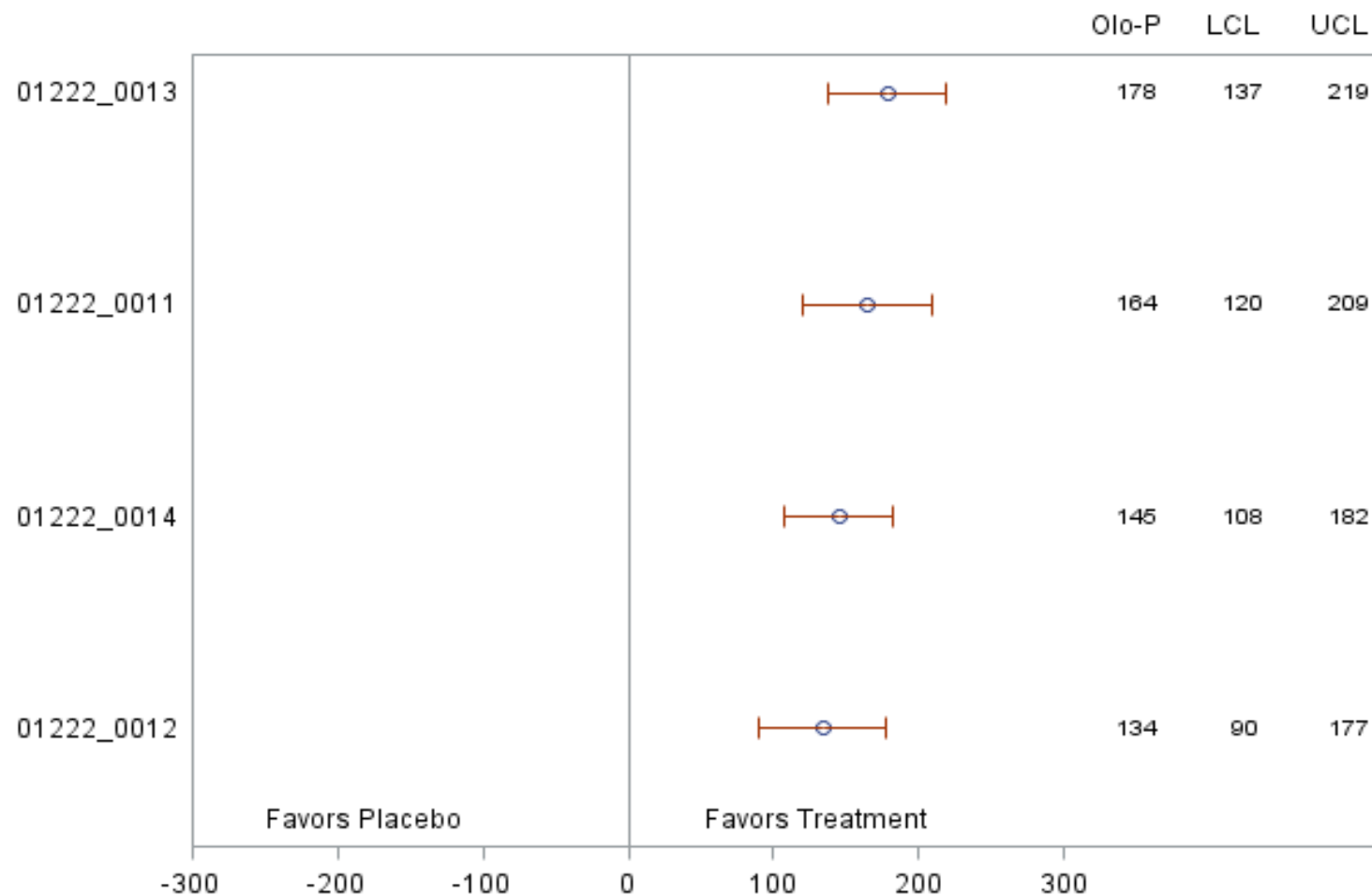
# 48 Week Spirometry Trials

- Design and Analysis
- Issues
- Results
  - Primary Endpoints (Week 12)
    - $\Delta$ Trough  $FEV_1$
    - $\Delta FEV_1 AUC_{0-3hr}$
  - Secondary Endpoints
    - $\Delta FEV_1 AUC_{0-12hr}$  (Week 12)
    - Incidence Moderate Exacerbations
    - SGRQ
- Interim Summary



# Primary Endpoint: Week 12 FEV<sub>1</sub> AUC<sub>0-3hr</sub> Response

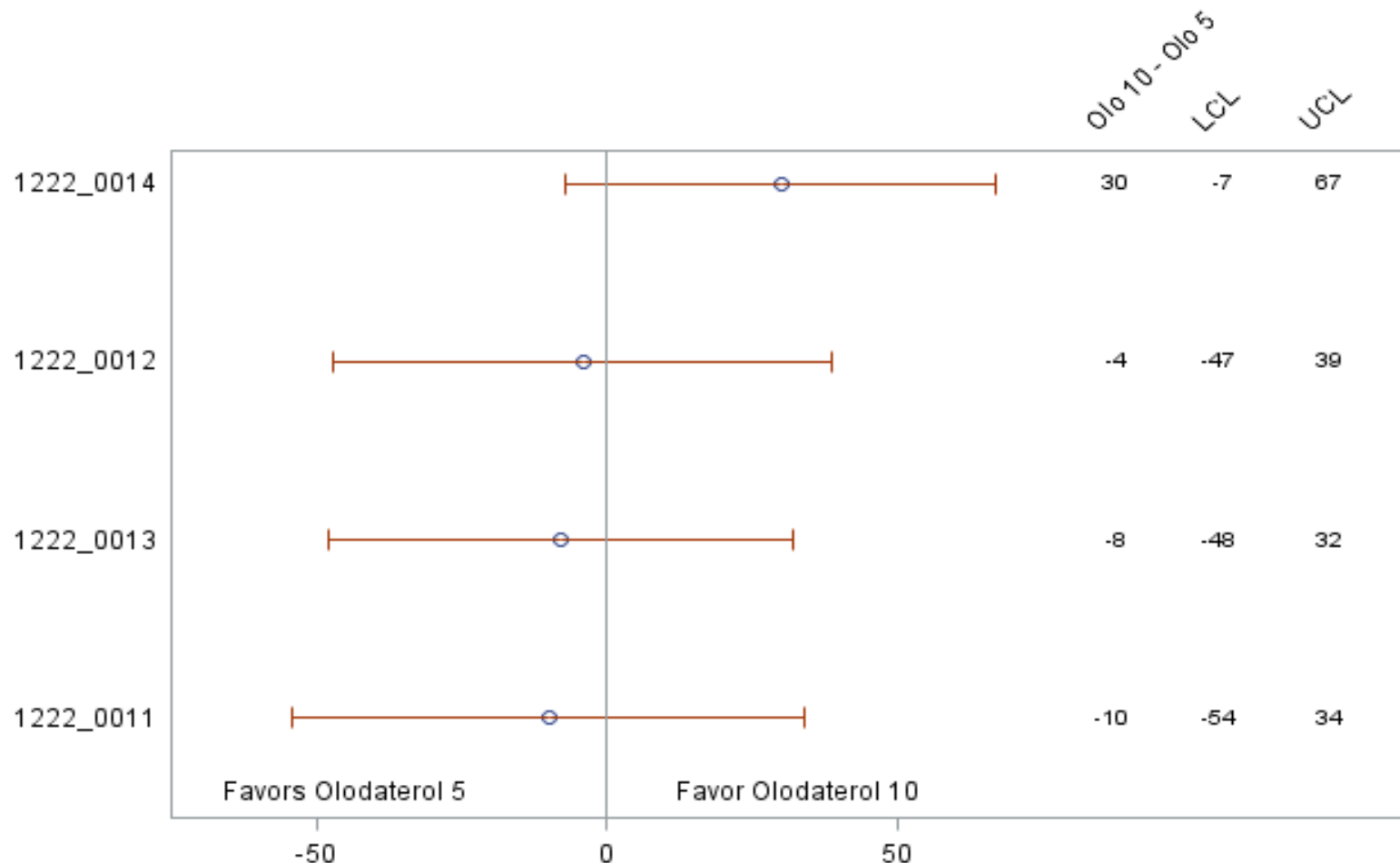
**AUC 0-3 hr Response at Week 12: Olodaterol 5 - Placebo (mL)**  
**With 95% CL**



# Primary Endpoint: Week 12

## FEV<sub>1</sub> AUC<sub>0-3hr</sub> Response (Olo 10 vs Olo 5)

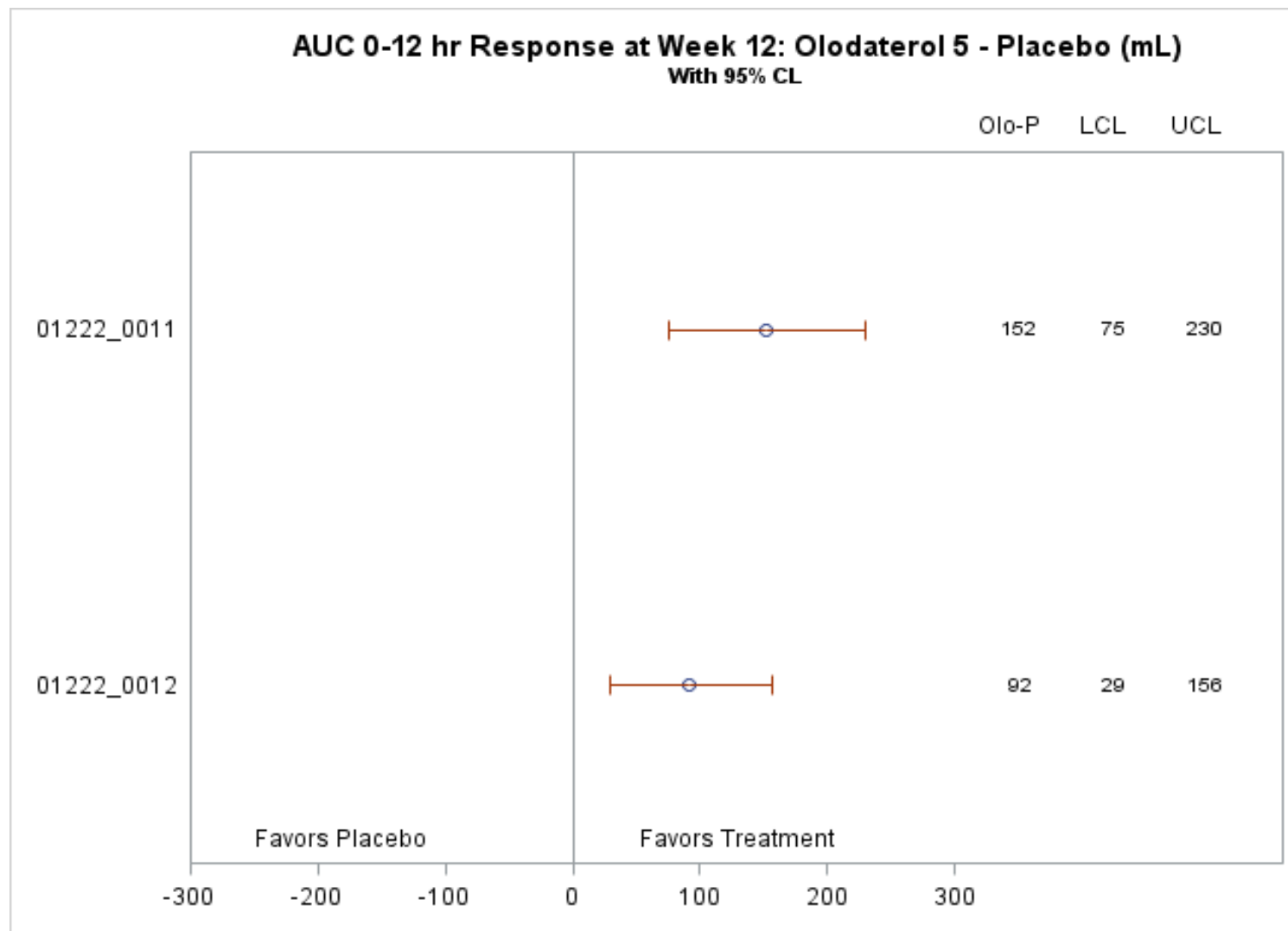
**AUC 0-3 hr at Week 12: Olodaterol 10 - Olodaterol 5 (mL)**  
**With 95% CL**



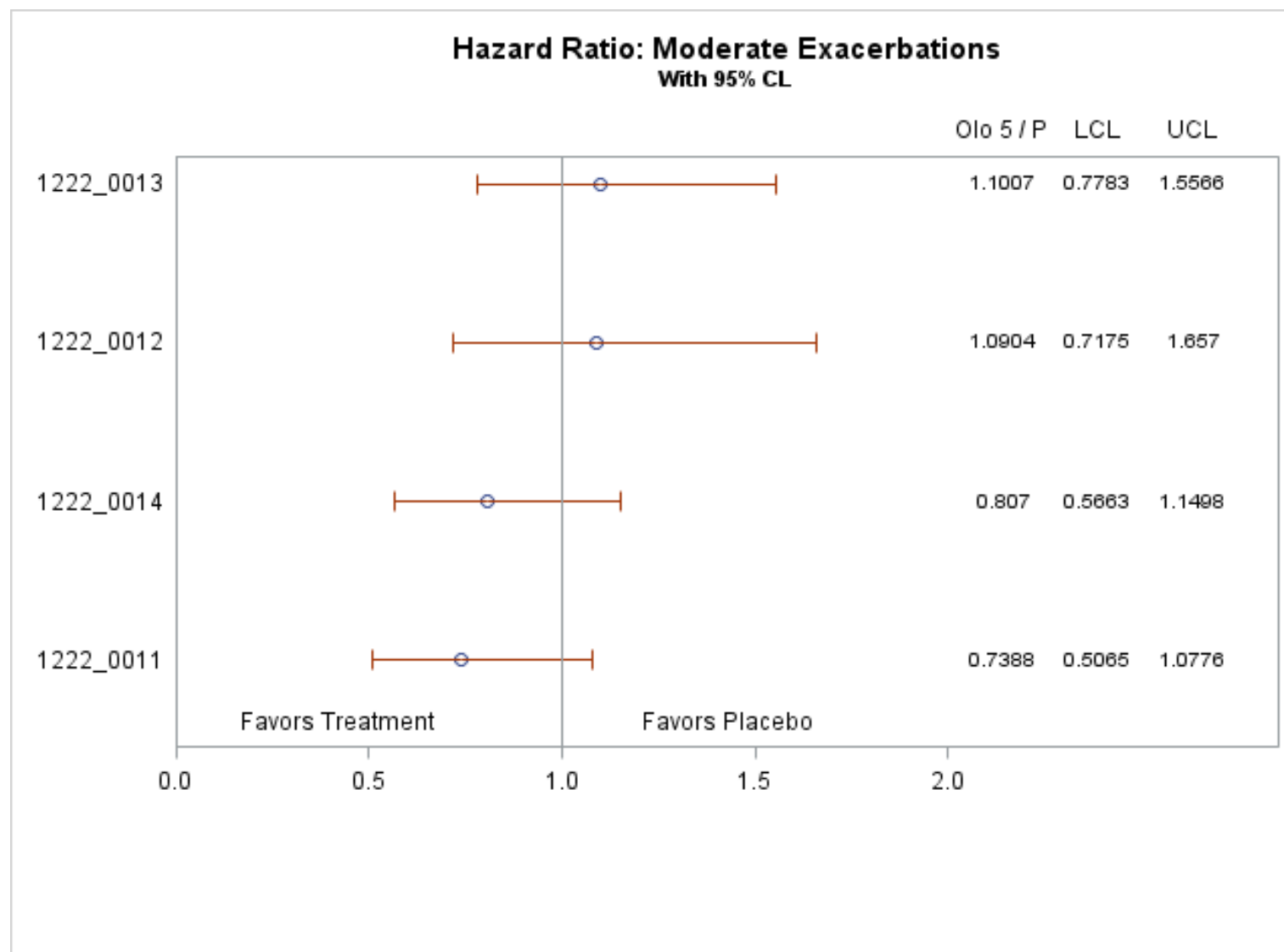
# 48 Week Spirometry Trials

- Design and Analysis
- Issues
- Results
  - Primary Endpoints (Week 12)
    - $\Delta$ Trough  $FEV_1$
    - $\Delta FEV_1 AUC_{0-3hr}$
  - Secondary Endpoints
    - $\Delta FEV_1 AUC_{0-12hr}$  (Week 12)
    - Incidence Moderate Exacerbations
    - SGRQ
- Interim Summary

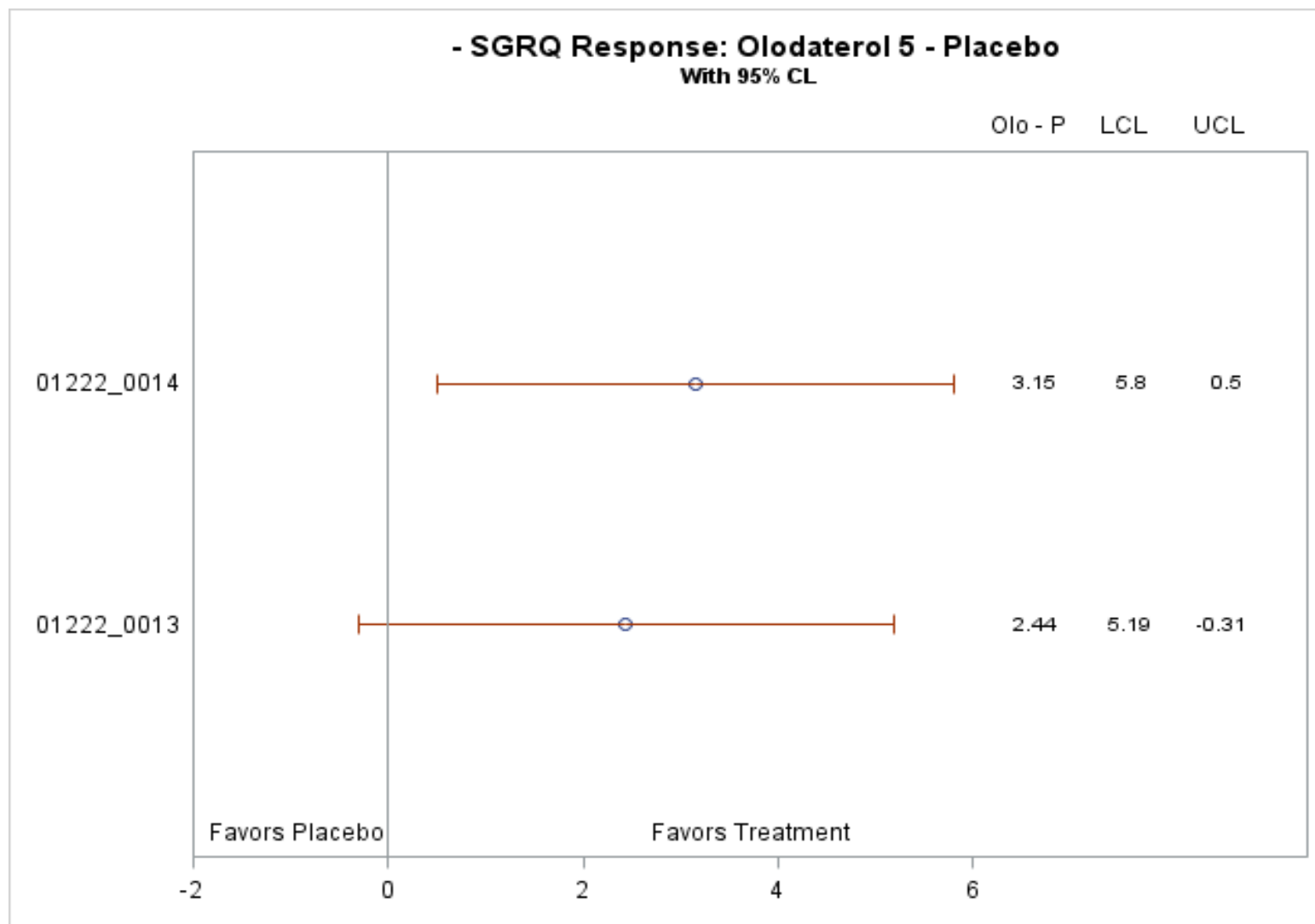
# Secondary Endpoint: Week 12 FEV<sub>1</sub> AUC<sub>0-12hr</sub> Response



# Secondary Endpoint: Moderate Exacerbations



# Secondary Endpoint: St. George Respiratory Questionnaire at Week 24



## Interim Summary: 48 Week Spirometry Trials

- Primary Endpoints
  - $\Delta$ Trough FEV<sub>1</sub>
    - Statistically significant in 3 of 4 studies
    - Average effect of olodaterol 5: 65 mL
  - $\Delta$  FEV1 AUC<sub>0-3hr</sub>
    - Statistically significant in 4 of 4 studies
    - Average effect of olodaterol 5: 155 mL
- Difference between olodaterol 5 and olodaterol 10
  - Not statistically significant

## Interim Summary: 48 Week Spirometry Trials

- Secondary Endpoints
  - $\Delta \text{FEV}_1 \text{ AUC}_{0-12\text{hr}}$ 
    - Nominally statistical significance in 4 of 4 studies
    - Average effect of olodaterol 5: 122 mL
  - Incidence Moderate Exacerbations
    - No statistically significant effect seen
  - SGRQ
    - Statistical significance in 1 of 2 studies
    - Effect in that study was -3.15



# Six Week Spirometry Trials

- Design and Analysis
- Issues
- Results
  - Primary Endpoint:  $\Delta \text{FEV}_1 \text{ AUC}_{12-24\text{hr}}$  at Week 6
- Interim Summary

# Statistical Analyses: 6 Week Spirometry

Study	Endpoints	Contrasts	Analysis
1222.24 1222.25 100% USA crossover	Primary (Week 6): $\Delta\text{FEV}_1$ AUC <sub>0-12hr</sub> $\Delta\text{FEV}_1$ AUC <sub>12-24hr</sub>  Secondary (Week 6): $\Delta\text{FEV}_1$ AUC <sub>0-24hr</sub>	Olo 10 v P Olo 5 v P  Olo 5 v F	MMRM  Trt, period, center, patient(center)
1222.39 1222.40 No USA crossover	Primary (Week 6): $\Delta\text{FEV}_1$ AUC <sub>0-12hr</sub> $\Delta\text{FEV}_1$ AUC <sub>12-24hr</sub>  Secondary (Week 6): $\Delta\text{FEV}_1$ AUC <sub>0-24hr</sub>	Olo 10 v P Olo 5 v P	MMRM  Trt, period, patient, baseline

# Issues

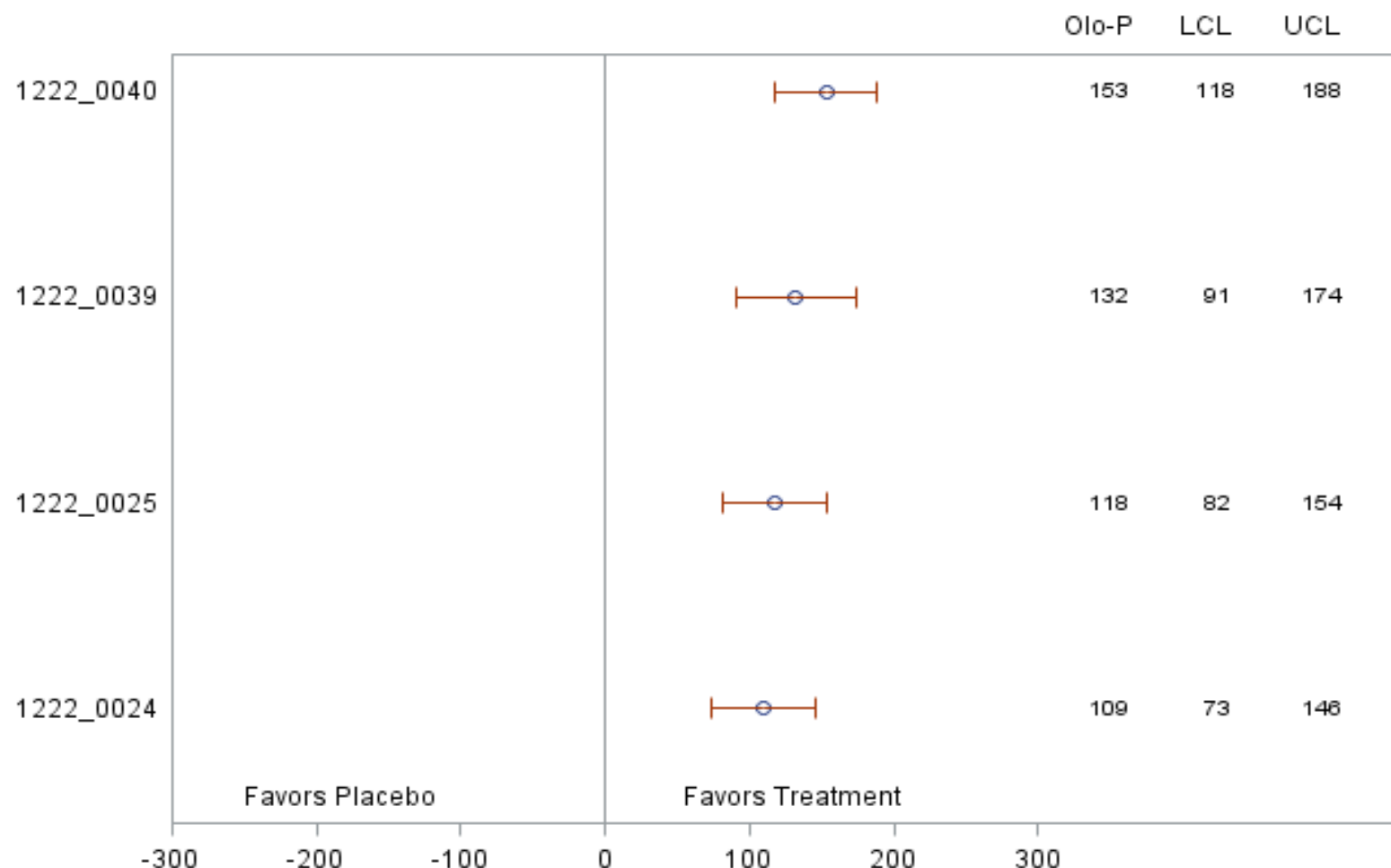
- $\Delta FEV_1$   $AUC_{12-24hr}$ 
  - Measured only at Week 6
  - Gaps in data

# Six Week Spirometry Trials

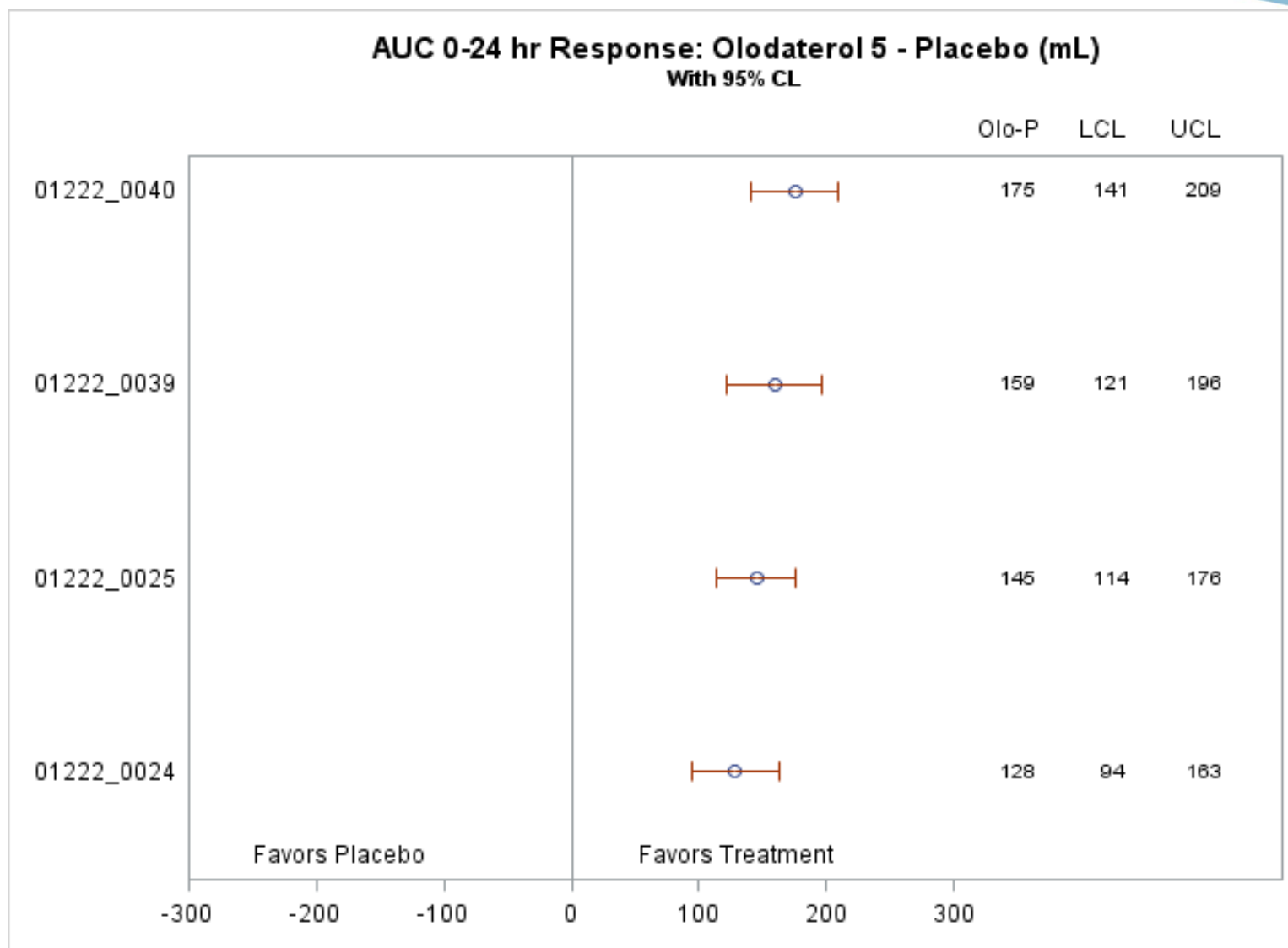
- Design and Analysis
- Issues
- Results
  - Primary Endpoint:  $\Delta FEV_1$   $AUC_{12-24hr}$  Week 6
- Interim Summary

# FEV<sub>1</sub> AUC<sub>12-24hr</sub> Response Week 6

**AUC 12-24 hr Response: Olodaterol 5 - Placebo (mL)**  
With 95% CL

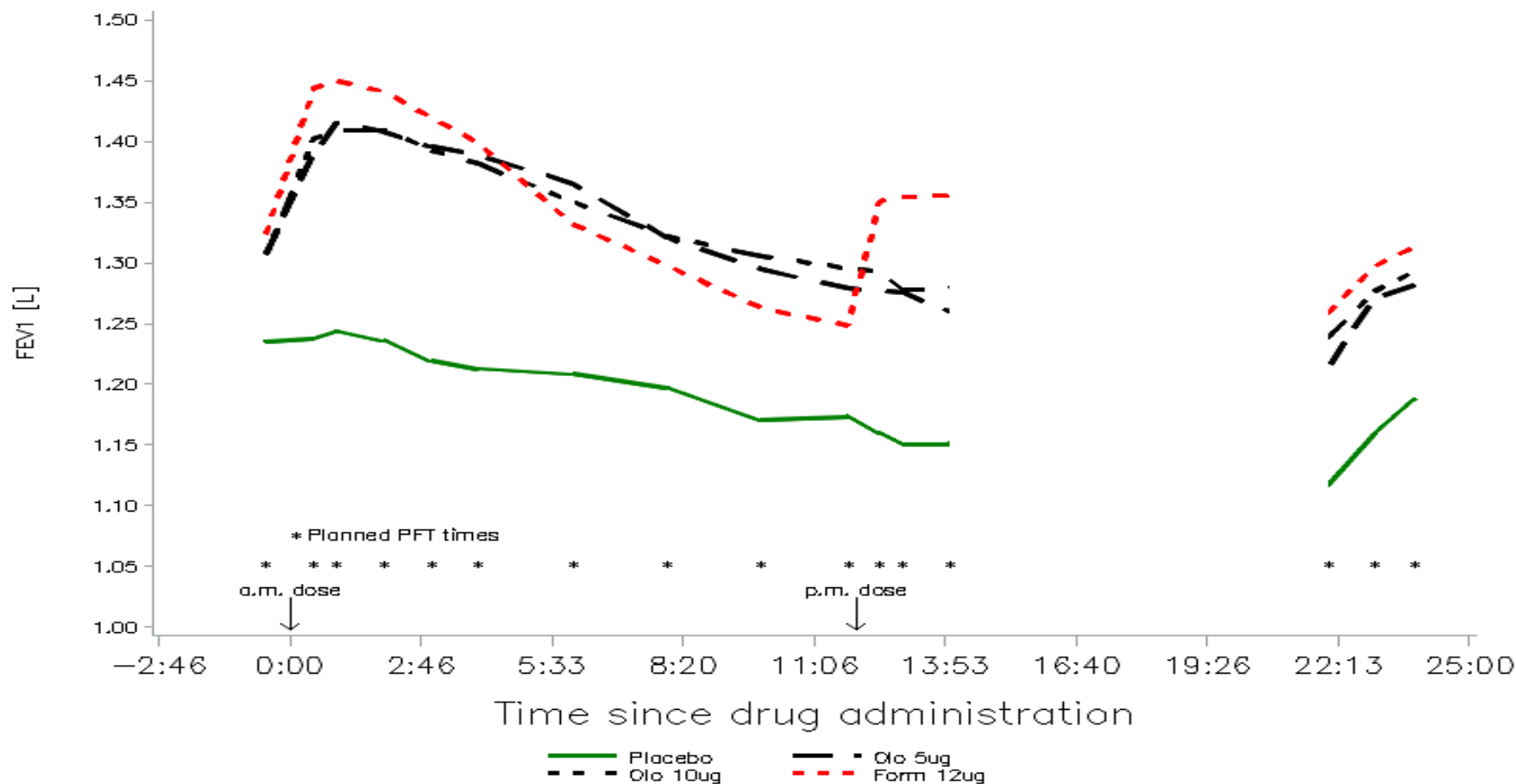


# FEV<sub>1</sub> AUC<sub>0-24hr</sub> Response Week 6

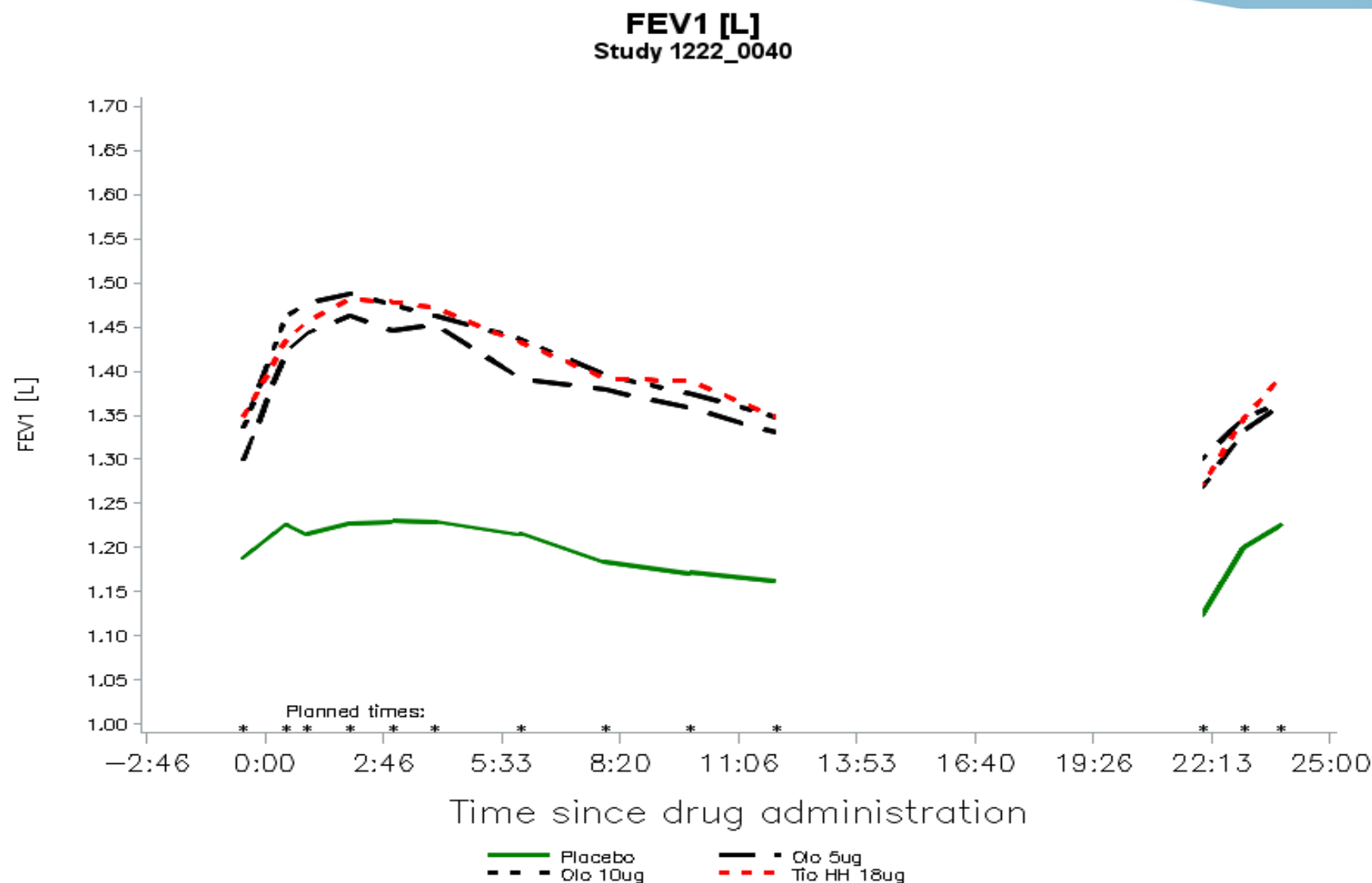


# FEV<sub>1</sub> Week 6: Data Collected

**FEV1 [L]**  
**Study 1222\_0024**



# FEV<sub>1</sub> Week 6: Data Collected





## Interim Summary: Six Week Spirometry Trials

- $FEV_1$   $AUC_{12-24hr}$  Week 6
  - Significant effect of olodaterol 5 at week 6
  - Quantification imprecise
    - Gap in available data

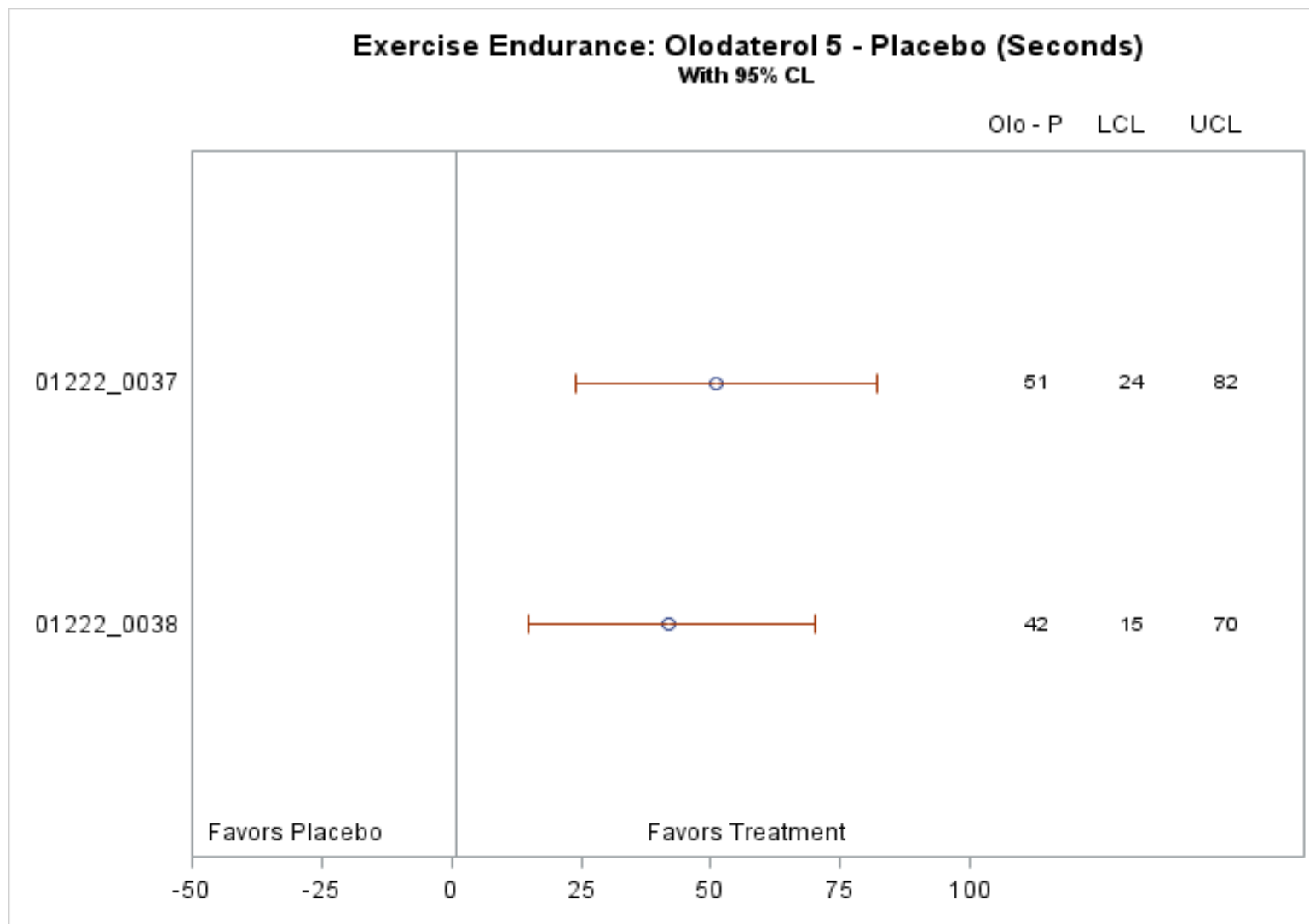
# Six Week Exercise Tolerance Trials

- Design and Analysis
- Results
  - Primary Endpoint: Exercise Endurance (Week 6)
  - Secondary Endpoint: IC at Isotime (Week 6)
- Interim Summary

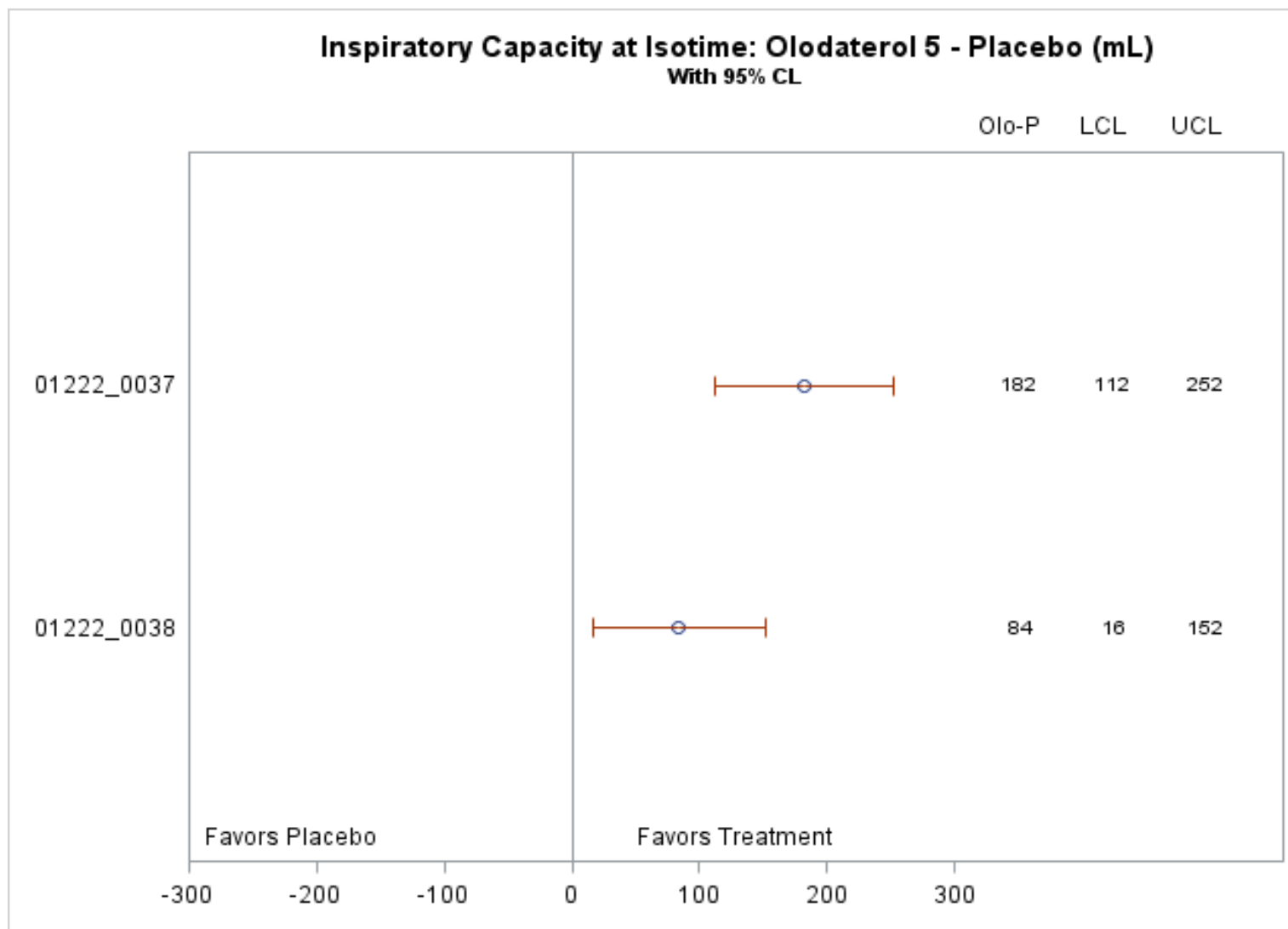
# Statistical Analyses: 6 Week Exercise Tolerance

Study	Endpoints	Contrasts	Analysis
1222.37 1222.38 No USA crossover	Primary (Week 6): Exercise endurance  Secondary (Week 6): IC at isotime Breathing discomfort intensity at isotime FRC	Olo 10 v P Olo 5 v P	MMRM  trt, period, baseline  response logged for primary

# Primary Endpoint: Exercise Endurance at Week 6



# Secondary Endpoint: Inspiratory Capacity at Isotime (Week 6)



## Interim Summary: Six Week Exercise Tolerance Trials

- Exercise Endurance
  - Statistically significant effects
- IC at Isotime
  - Statistically significant effects

# Outline

- Design, Issues, Results, and Interim Summaries for
  - Parallel Arm Spirometry Studies
  - Six Week Spirometry Trials
  - Six Week Exercise Tolerance Trials
- Subgroup Analyses
- Summary

## Subgroup Analyses 48 Week Spirometry Trials: Trough $FEV_1$ and $FEV_1$ $AUC_{0-3hr}$ at Week 12

- Race, US residence
  - No significant effect on treatment
- Age
  - Benefit of olodaterol greater if age less than 50 yrs for  $FEV_1$   $AUC_{0-3hr}$



# Submission Summary

Endpoint	Significance	Average Effect
Trough FEV <sub>1</sub> Week 12	3 of 4 studies	65 mL
$\Delta$ FEV <sub>1</sub> AUC <sub>0-3hr</sub> Week 12	Y	155 mL
$\Delta$ FEV <sub>1</sub> AUC <sub>0-12hr</sub> Week 12	nominal only	122 mL
$\Delta$ FEV <sub>1</sub> AUC <sub>12-24hr</sub> Week 6	Y	unknown
$\Delta$ FEV <sub>1</sub> AUC <sub>0-24hr</sub> Week 6	Y	unknown
SGRQ Week 24	1 of 2 studies	-3.15*
Moderate Exacerbations	N	
Exercise Endurance Week 6	Y	47 sec
IC at Isotime Week 6	Y	130 mL

No significant differences between olodaterol 10 and olodaterol 5

\* Value for the significant study



# Thank You

# Outline

- Overview of the Clinical Program

*Robert Lim, MD*

*Clinical Reviewer, DPARP, CDER, FDA*

- Statistical Review of Efficacy

*Robert Abugov, PhD*

*Statistical Reviewer, DB II, CDER, FDA*

- Clinical Review of Efficacy, Safety, Risk/Benefit

*Robert Lim, MD*

*Clinical Reviewer, DPARP, CDER, FDA*

# Outline

- Efficacy
  - Bronchodilation
  - Exercise Tolerance
- Safety
  - Definitions
  - Class Safety Concerns
  - Extent of Exposure
  - Main Safety Results
    - Deaths
    - Serious Adverse Events (SAEs)
    - Common Adverse Events
    - Respiratory Adverse Events
    - Cardiac Adverse Events
    - Neoplasm
- Risk/Benefit

# Efficacy- Bronchodilation

<b>Trial Year Completed</b>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Primary Endpoints</b>	<b>Sites</b>
1222.11 2010	R, DB, PC, PG 48-week treatment	625	Olo 5mcg qD Olo 10mcg qD Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 At 12 weeks	Europe, Asia, Australia, New Zealand, US (54 sites)
1222.12 2010	R, DB, PC, PG 48-week treatment	644	Olo 5mcg qD Olo 10mcg qD Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 At 12 weeks	Europe, Asia, US (52 sites)
1222.13 2010	R, DB, DD, PC, PG 48-week treatment	906	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 TDI At 24 weeks	Europe, Asia, Africa (94 sites)
1222.14 2010	R, DB, DD, PC, PG 48-week treatment	937	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 TDI At 24 weeks	Europe, Asia, Africa (103 sites)

Key: N=randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, DD= double-dummy PC=placebo control, PG=parallel group, AC=active control, CO=crossover, TDI=transitional dyspnea index

## Efficacy- Bronchodilation

- Treatment effect (5mcg qD)
  - Mean trough FEV1 effect @12 wks was 65mL
    - Range 33 - 84mL
  - Mean FEV1 AUC(0-3hr) effect @12 wks was 155mL
    - Range 134 - 178mL
  - No benefit of the 10mcg dose over 5mcg
  - Patients were allowed continue maintenance COPD medications during trial except LABAs

# Efficacy- Exercise Tolerance

<b>Trial Year Completed</b>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Pertinent Endpoints</b>	<b>Sites</b>
1222.37 2011	R, DB, PC, CO 6-week treatment	151	Olo 5mcg qD Olo 10mcg qD Placebo	Endurance time Inspiratory capacity	Europe, Canada, Australia (16 sites)
1222.38 2011	R, DB, PC, CO 6-week treatment	157	Olo 5mcg qD Olo 10mcg qD Placebo	Endurance time Inspiratory capacity	Europe, Canada (16 sites)

Key: N=Randomized patients, Olo=olodaterol, R=randomized, DB=double-blind, PC=placebo-control, CO=crossover

## Efficacy- Exercise Tolerance

<b>Olodaterol 5mcg</b>	<b>Improvement in ET compared to placebo</b>	<b>IC at isotime (mL) Difference from placebo</b>
Trial 1222.37	14% (51 s)	↑182
Trial 1222.38	12% (42 s)	↑ 84
Statistical significance	yes	yes

Key: ET=endurance time; IC=inspiratory capacity

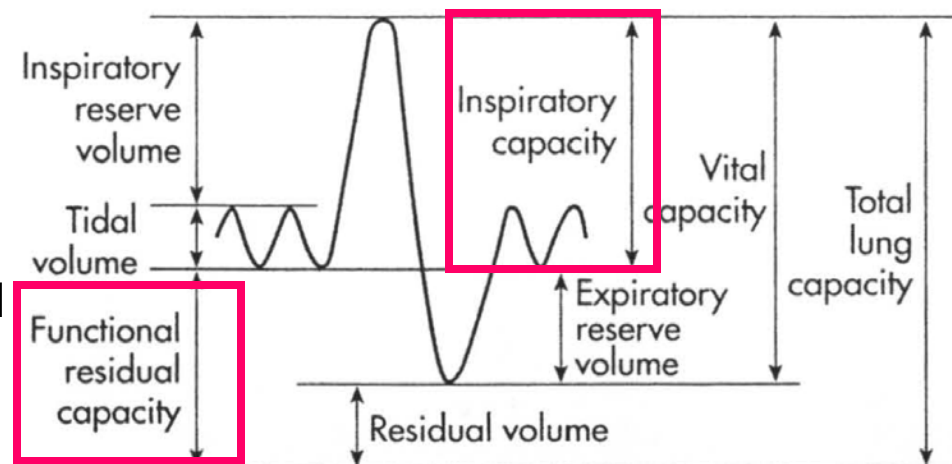


# Cardiopulmonary Exercise Testing

- Provides a global assessment of the integrative exercise response
  - Pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems
- Cycle ergometry is the preferred mode of testing
  - Work rate is easily quantifiable
- Maximal incremental protocols
  - Incremental increases in work until the patient reaches exhaustion
- Constant work rate protocols
  - Performed at a set percentage of the maximal work rate determined during incremental testing

# Hyperinflation

- Airway obstruction
- Progressive hyperinflation
  - Decreased Inspiratory Capacity
  - Increased Functional Residual Capacity
- Exaggerated during exercise
- Hyperinflation plays a key role in exercise limitation



# Issues with Exercise Tolerance Trials

- Generalizability
- Minimum Clinically Important Difference (MCID)
- Timing

# Generalizability

- Must be able to complete cycle ergometry testing
  - Arthritis
  - Orthopedic injuries
  - Poor coordination
- Exercise performance limitation not related to exertional dyspnea or fatigue
  - Morbid obesity
  - Claudication
  - Angina pectoris

# Lack of MCID

	<b>Puente-Maestu <i>et al</i> (2009)</b>	<b>Laviolette <i>et al</i> (2009)</b>
Intervention	8-weeks of pulmonary rehabilitation	6-12 weeks of pulmonary rehabilitation
Testing	CWRCE at 75% maximal workload	CWRCE at 80% maximal workload
Endurance time	101 second improvement (34%) ('slightly better')	153 second improvement (SGRQ≥4)

CWRCE=constant work rate cycle ergometry

# Lack of MCID

	<b>Puente-Maestu <i>et al</i> (2009)</b>	<b>Laviolette <i>et al</i> (2008)</b>		<b>1222.37 1222.38</b>
Intervention	8-weeks of pulmonary rehabilitation	6-12 weeks of pulmonary rehabilitation		6-week of Olodaterol
Testing	CWRCE at 75% maximal workload	CWRCE at 80% maximal workload		CWRCE at 75% maximal workload
Endurance time	101 second improvement (34%) (‘slightly better’)	153 second improvement (SGRQ≥4)		40-50 second difference from placebo

CWRCE=constant work rate cycle ergometry

- No accepted MCID for inspiratory capacity

# Timing

- Adequacy of trial length
  - Unclear if a 6-week treatment period is sufficient to fully characterize treatment effect
  - $\geq 3$  months for airflow obstruction<sup>‡</sup>
  - $\geq 6$  months for symptom relief<sup>‡</sup>
  - $\geq 12$  months for preventing exacerbation<sup>‡</sup>
- Exercise testing performed 2-hours after morning dose
  - Sustainability of endurance time and inspiratory capacity effect over 24-hour dosing interval

<sup>‡</sup>FDA Guidance for Industry COPD: Developing Drugs for Treatment (2007).

# Safety Considerations

- Class Safety Concerns
- Extent of Exposure
- Main Safety Results
  - Deaths
  - Serious Adverse Events (SAEs)
  - Common Adverse Events
  - Respiratory Adverse Events
  - Cardiac Adverse Events
  - Neoplasm
- Risk/Benefit



## Class Safety Concerns

- LABAs have been associated with increased risk of severe exacerbations and asthma-related deaths
  - Boxed Warning and Medication Guide for all marketed LABAs
  - LABA use contraindicated without concomitant use of another asthma controller medication
  - Sponsors of LABA products with asthma indications are being required to perform large safety trials
- A similar safety signal has not been observed in COPD patients

## Overall Extent of Exposure

- 3353 COPD patients exposed to olodaterol
  - 2334 COPD patients exposed in parallel group trials
    - 1522 patient years
  - 1019 COPD patients exposed in cross-over trials
    - 199 patient years
  - Majority of exposure from 48-week spirometry trials

# Primary Safety Database

<b>Trial Year Completed</b>	<b>Design</b>	<b>N</b>	<b>Treatment</b>	<b>Primary Endpoints</b>	<b>Sites</b>
1222.11 2010	R, DB, PC, PG 48-week treatment	208 207 209	Olo 5mcg qD Olo 10mcg qD Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 At 12 weeks	Europe, Asia, Australia, New Zealand, US (54 sites)
1222.12 2010	R, DB, PC, PG 48-week treatment	209 217 216	Olo 5mcg qD Olo 10mcg qD Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 At 12 weeks	Europe, Asia, US (52 sites)
1222.13 2010	R, DB, DD, PC, PG 48-week treatment	227 225 227 225	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 TDI At 24 weeks	Europe, Asia, Africa (94 sites)
1222.14 2010	R, DB, DD, PC, PG 48-week treatment	232 234 233 235	Olo 5mcg qD Olo 10mcg qD Formoterol Placebo	FEV1 AUC (0 - 3hrs) Trough FEV1 TDI At 24 weeks	Europe, Asia, Africa (103 sites)

Key: N=patients who have received at least one dose, Olo=olodaterol, R=randomized, DB=double-blind, DD= double-dummy PC=placebo control, PG=parallel group, AC=active control, CO=crossover, TDI=transitional dyspnea index

## Extent of Exposure -48 week spirometry trials

	Placebo	Olo 5mcg	Olo 10mcg	Formoterol
<b>Overall Treatment Duration (days)</b>				
Number of patients	885	876	883	460
Mean (SD)	287.5 (104)	308.4 (78.4)	304.7 (84.8)	299.0 (94.1)
<b>Treatment Duration, n(%)</b>				
≥85 days (12 weeks)	793 (89.6)	833 (95.1)	828 (93.8)	420 (91.3)
≥ 169 days (24 weeks)	748 (84.5)	792 (90.4)	798 (90.4)	403 (87.6)
≥ 330 days (47 weeks)	686 (77.5)	741 (84.6)	733 (83.0)	376 (81.7)
≥ 337 days (48 weeks)	469 (53.0)	504 (57.5)	510 (57.8)	259 (56.3)

SCS supplement; table 1.10; pg 690

# Death

	<b>Placebo N=885</b>	<b>Olo 5mcg N=876</b>	<b>Olo 10mcg N=883</b>	<b>Formoterol N=460</b>
Total Deaths (%)	23 (2.7)	19 (2.2)	21 (2.4)	13 (2.8)
On-treatment (%)	13 (1.5)	13 (1.5)	17 (1.9)	10 (2.2)
Vital status follow-up (%)	10 (1.1)	5 (0.6)	4 (0.5)	2 (0.4)
After vital status follow-up (%)	0	1 (0.1)	0	1 (0.2)

Trial 1222.11 CSR; tables 12.3.1:1 and 12.3.1:2; pp 108 and 109

Trial 1222.12 CSR; tables 12.3.1:1 and 12.3.1:2; pp 114 and 115

Trial 1222.13 CSR; tables 12.3.1:1 and 12.3.1:2; pp 128 and 129

Trial 1222.14 CSR; tables 12.3.1:1 and 12.3.1:2; pp 123 and 124

## On-Treatment Deaths (adjudicated)

Cause of death	Placebo N=885	Olo 5mcg N=876	Olo 10mcg N=883	Formoterol N=460
<b>Total deaths, n (%)</b>	13 (1.5)	13 (1.5)	17 (1.9)	10 (2.2)
COPD exacerbation	4 (0.5)	9 (1.0)	4 (0.5)	3 (0.7)
Sudden cardiac death	2 (0.2)	2 (0.2)	0 (0)	3 (0.7)
Unknown	3 (0.3)	0 (0)	2 (0.2)	1 (0.2)
Lung cancer	0	1 (0.1)	4 (0.5)	1 (0.2)
Pneumonia	0	0	2 (0.2)	0
Hepatic carcinoma	0	1 (0.1)	0	0
Esophageal carcinoma	0	0	1 (0.1)	0
Laryngeal carcinoma	0	0	1 (0.1)	0
Bladder carcinoma	0	0	1 (0.1)	0
Congestive heart failure	0	0	1 (0.1)	0
Suicide	0	0	1 (0.1)	0

SCS; table 2.1.3.2.1:2; pp 67-68

# Serious Adverse Events

SOC/PT	Placebo N=885	Olo 5mcg N=885	Olo 10mcg N=883	Formoterol N=460
<b>Total with SAE, n (%)</b>	145 (16.4)	138 (15.8)	147 (16.6)	69 (15)
COPD	53 (6.0)	41 (4.7)	60 (6.8)	27 (5.9)
Pneumonia	13 (1.5)	14 (1.6)	22 (2.5)	7 (1.5)
Atrial fibrillation	3 (0.3)	5 (0.6)	5 (0.6)	1 (0.2)
Respiratory failure	7 (0.8)	2 (0.2)	3 (0.3)	0 (0.0)
Pneumothorax	5 (0.6)	2 (0.2)	3 (0.3)	1 (0.2)
Infective exacerbation of COPD	4 (0.5)	2 (0.2)	1 (0.1)	2 (0.4)
Coronary artery disease	3 (0.3)	3 (0.3)	2 (0.2)	0 (0.0)
Acute respiratory failure	2 (0.2)	3 (0.3)	2 (0.2)	1 (0.2)
Acute myocardial infarction	2 (0.2)	1 (0.1)	4 (0.5)	0 (0.0)
Dyspnea	3 (0.3)	1 (0.1)	1 (0.1)	2 (0.4)
Fall	1 (0.1)	2 (0.2)	4 (0.5)	0 (0.0)

SCS; table 2.1.4.1.1:1; pg 73

## Common Treatment Emergent Adverse Events

Preferred term	Placebo N=885	Olo 5mcg N=885	Olo 10mcg N=883	Formoterol N=460
<b>Total with AE, n (%)</b>	627 (71)	622 (71)	642 (73)	318 (69)
COPD	255 (29)	227 (26)	266 (30)	131 (29)
Nasopharyngitis	68 (8)	99 (11)	91 (10)	46 (10)
Upper respiratory tract infection	66 (8)	72 (8)	62 (7)	32 (7)
Bronchitis	32 (4)	41 (5)	31 (4)	13 (3)
Cough	35 (4)	37 (4)	35 (4)	27 (6)
Pneumonia	24 (3)	22 (3)	35 (4)	14 (3)
Back pain	24 (3)	31 (4)	28 (3)	18 (4)

SCS; table 2.1.2.1.1:1; pg 54



# Respiratory Safety

- Assessment of respiratory safety included:
  - An analysis based on sponsor defined pharmacovigilance endpoints
    - Consisted of preferred terms (PT) grouped by similar concepts, that did not necessarily correspond to MedDRA system organ class (SOC) or high level grouping terms (HLGT)
  - An adjudicated analysis SAEs specifically evaluating for respiratory-related events
    - Examined all trials with treatment durations >7 days
      - Parallel group trials in COPD and asthmatics
      - First treatment period in cross-over trials
    - Analysis performed in total population and separately in the COPD and asthma populations

## Respiratory Safety (continued)

- Pharmacovigilance analysis
  - Consistent with SAE and TEAE analysis
- Adjudicated analysis
  - COPD population
    - Consistent with previous analysis
  - Asthma population
    - 512 asthmatics exposed
    - Single respiratory related hospitalization (Olo 10mcg)
    - No deaths, no intubations

# Cardiac Safety

- Assessment of CV risk included:
  - An analysis of major adverse cardiac events (MACE):
    - Cardiac disorder death
    - Vascular disorder death
    - Standard MedDRA query (SMQ) Ischemic heart disease sub SMQ myocardial infarction
    - Stroke pharmacovigilance endpoint (defined by BI)
    - Sudden death, cardiac death, and sudden cardiac death preferred terms
  - An analysis based on multiple cardiac related standard MedDRA queries (SMQs)

## MACE analysis- all events

	Placebo N=885	Olo 5 mcg N=876	Olo 10mcg N=883	Formoterol N=460
<b>MACE (any), n (%)</b>				
Cardiac disorder SOC (fatal)	3 (0.3)	2 (0.2)	1 (0.1)	3 (0.7)
Vascular disorder SOC (fatal)	1 (0.1)	0	0	1 (0.2)
SMQ Ischemic heart disease sub-SMQ myocardial infarction (any)	9 (1.0)	4 (0.5)	12 (1.4)	4 (0.9)
Stroke Pharmacovigilance endpoint (any)	11 (1.2)	3 (0.3)	3 (0.3)	1 (0.2)
Sudden death PT	1 (0.1)	0	0	1 (0.2)
Cardiac death PT	0	0	0	0
Sudden cardiac death PT	0	1 (0.1)	1 (0.1)	0

Table A.1:1;Clinical response to IR dated 11/13/2012

# Cardiac SMQs

Standardized MedDRA Queries (v.14.1)	Placebo N=885	Olo 5 mcg N=876	Olo 10mcg N=883	Formoterol N=460
<b>Total with adverse events, n (%)</b>	627 (71)	622 (71)	642 (73)	318 (69)
SMQ Cardiac Arrhythmia				
sub– SMQ Cardiac arrhythmia terms	37 (4.2)	49 (5.6)	39 (4.4)	20 (4.3)
sub– SMQ Tachyarrhythmias	30 (3.4)	31 (3.5)	26 (2.9)	15 (3.3)
sub– SMQ Ventricular tachyarrhythmias	9 (1.0)	17 (1.9)	12 (1.4)	9 (2.0)
SMQ Ischemic heart disease sub–SMQ Myocardial infarction (broad)	9 (1.0)	4 (0.5)	12 (1.4)	4 (0.9)
SMQ Cardiac failure (narrow)	5 (0.6)	11 (1.3)	7 (0.8)	1 (0.2)
SMQ Torsades de pointes/ QT– prolongation (narrow)	6 (0.7)	11 (1.3)	4 (0.5)	5 (1.1)

SCS supplement; table 2.8.2.1; pp 1004-1009

# Neoplasm

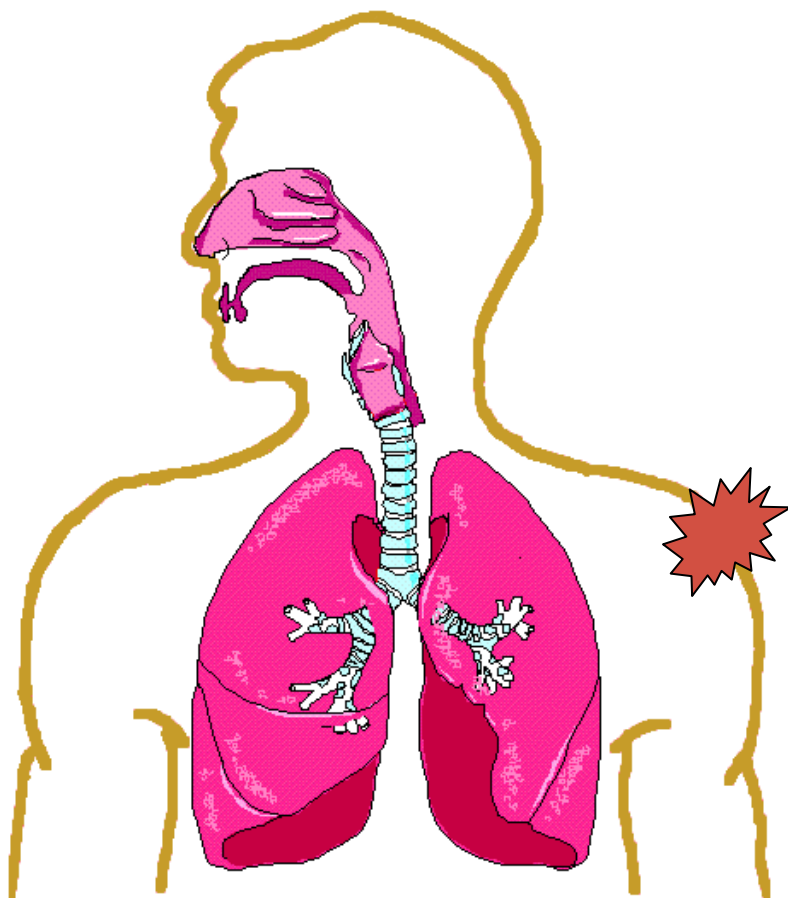
SOC/PT	Placebo N=885	Olo 5mcg N=876	Olo 10mcg N=883	Formoterol N=460
<b>Total Adverse Events, n (%)</b>				
<b>Neoplasms benign, malignant and unspecified</b>	14 (1.6)	22 (2.5)	32 (3.6)	11 (2.4)
<b>Deaths</b>				
Neoplasms benign, malignant and unspecified	0 (0.0)	2 (0.2)	7 (0.8)	1 (0.2)
Lung neoplasm malignant	0	1 (0.1)	1 (0.1)	0
Small cell lung cancer stage unspecified	0	0	2 (0.2)	0
Lung adenocarcinoma	0	0	1 (0.1)	1 (0.2)
<b>SAEs</b>				
Neoplasms benign, malignant and unspecified	9 (1.0)	14 (1.6)	19 (2.2)	8 (1.7)
Lung neoplasm malignant	0 (0.0)	1 (0.1)	2 (0.2)	2 (0.4)
Small cell lung cancer stage unspecified	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)
Lung adenocarcinoma	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.2)

SCS; table 2.1.3.2.1:2; pp 67-68; table 2.1.3.2.1:1; pp 64-65; table 2.1.4.1.1:1; pg 73

# Risk/Benefit

- Benefit
  - Bronchodilator
  - Exercise Tolerance??
    - Generalizability
    - Lack of MCID
    - Timing
- Risk
  - Typical for a LABA
  - Numerical imbalance in neoplasms

## Division of Pulmonary, Allergy and Rheumatology Products





# Pulmonary Allergy Drugs Advisory Committee Meeting Olodaterol Inhalation Spray NDA 203108

Theresa M. Michele, MD  
Clinical Team Leader  
Division of Pulmonary, Allergy, and Rheumatology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
January 29, 2013

## Topics for Discussion

- Efficacy data
  - Bronchodilation
  - Exercise Tolerance
- Safety data

## Approval of an Application

### - 21 CFR 314.105 (c)

“FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling”

## Efficacy Standard

### - 21 CFR 314.125 Refusal to Approve an Application

(b) (5) “... substantial evidence consisting of adequate and well-controlled investigations ... that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”

# Safety Standard

## - 21 CFR 314.125 Refusal to Approve an Application

(b) (2) "... do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b) (3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b) (4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

## Question 1

### Discussion

Discuss the bronchodilator efficacy data for olodaterol.

## Question 2

### Discussion

Discuss the overall safety profile of olodaterol.

## Question 3

### Discussion

Discuss the proposed exercise claims for olodaterol, including the following:

- design of trials (e.g. duration, timing of medication and exercise testing)
- minimum clinically important difference for exercise endurance, and
- increased inspiratory capacity (IC) during exercise



## Question 4

### Voting

Considering the totality of the data, has olodaterol demonstrated substantial evidence of efficacy for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema?

### **(Voting question)**

- If not, what further data should be obtained?

## Question 5

### Voting

Is the safety profile of olodaterol adequate for approval for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema? **(Voting question)**

- If not, what further data should be obtained?

## Question 6

### Voting

Based on the information included in the briefing materials and presentations, has the applicant provided sufficient efficacy and safety data to support marketing of olodaterol inhalation solution for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema?  
**(Voting question)**

- If not, what further data should be obtained?

*Thank You!*